Delirium

in Intensive Care Patients

detection, impact, prediction, prevention, and biomarkers

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van de Medische Wetenschappen

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Promotores

Prof. dr. P. Pickkers
Prof. dr. J.G. van der Hoeven
Prof. dr. T. van Achterberg

Copromotor

Dr. L. Schoonhoven

Manuscriptcommissie

Prof. dr. M.G.M. OldeRikkert (vz)
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Knowing is not enough, we must apply
Willing is not enough, we must do

Es ist nicht genug, zu wissen, man muss auch anwenden
Es ist nicht genug, zu wollen, man muss auch tun

Johann Wolfgang von Goethe (1749 – 1832)

Contents

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Introduction and outline of this thesis

Delirium in Patients admitted to the Intensive Care

Definition of Delirium

The word delirium is derived from the Latin "lira" meaning track or trail. Delirium can be translated in terms of "derailment" or "to get off track". Delirium is a psycho-organic disorder, which implies that a physical cause underlies the cognitive dysfunction, whereas the symptoms are psychological. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) the diagnostic criteria for delirium are (1):

- Acute onset (hours or, days) and often fluctuating throughout the day
- Disturbances in consciousness: reduced clarity of awareness of the environment with a decreased attention span, reduced ability to focus, sustain and shift attention
- Change in cognition (memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not accounted for by a pre-existing, established, or evolving dementia
- From the history, physical examination, or laboratory findings there is evidence that the perceptual disturbance is caused by the direct physiological consequences of a general medical condition.

Incidence of Delirium in Intensive Care Patients

Delirium is a serious condition in hospitalized patients, including the critically ill patients in the Intensive Care Unit (ICU). In ICU patients, reported incidences range widely between 11-89% (2-4). These large differences in delirium incidence rates may be related to differences in ICU patient case-mix and is likely related to the intensity of the screenings and different methods of screening (5).

Three subtypes of delirium can be distinguished (4):

1. Hyperactive subtype: the patient is hyperalert or agitated
2. Hypoactive subtype: the patient is hypoalert or lethargic
3. Alternating or mixed subtype: characterized by alternating hyper- and hypoactive symptoms.

The hyperactive subtype, usually associated with delusions, hallucinations, agitation and disorientation, occurs in approximately 1-2% of patients with delirium (4). The hypoactive subtype, characterized by lethargy, psychomotor slowing and inappropriate speech or mood, occurs in approximately 35% of patients with delirium (4). In intensive care patients with delirium, the alternating or mixed subtype has the highest incidence rate, and represents up to 60-70% of all cases of delirium. Especially, the hypoactive subtype is difficult to recognize and the

incidence/prevalence is therefore likely to be underreported. Because of the fluctuating course of delirium it can be assumed that the alternating subtype is also underreported.

Detection of Delirium in Intensive Care Patients

The gold standard for diagnosing delirium is the examination by a psychiatrist/ neurologist or geriatrician, who assesses delirium based on the above-mentioned DSM-IV criteria. In clinical ICU practice this is barely feasible, especially considering the fluctuating course of delirium and the fact that symptoms are more often manifest outside office hours, after sundown (1;6). The most practical solution to this problem is recognition of delirium by the attending nurse. After all, of all caregivers, nurses spend most hours at the patient's bedside and are in the best position to closely observe the patient's behaviour for longer periods. However, evidence indicates that nurses, as well as physicians, often fail to identify delirium, especially the hypoactive- and the alternating subtypes (7). According to Inouye et al. (8), the most important reason for this is the lack of a practical delirium assess tool. Other studies confirm this, showing that if ICU patients are not screened for delirium in a standard manner, 60 to 70% of patients with delirium are missed by ICU nurses and physicians (9;10). As a result several assessment tools for ICU patients have been developed that facilitate early detection of delirium by professionals other than psychiatrists, neurologists or geriatrician. Of these delirium assessment tools for ICU patients the Intensive Care Delirium Screening Checklist (ICDSC) developed by Bergeron (11) and the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) designed by Ely et al. (12) are the most frequently used tools. The ICDSC is an observational instrument consisting of eight items with a sensitivity of 99% and a specificity of 64% (11). This implies that in 36% of the patients the test result show 'delirium', while DSM-IV criteria indicate that the patients are not suffering from delirium. The CAM-ICU, when used by dedicated research nurses, has a better performance with a sensitivity of 95-100% and a specificity of 93-98% (13). Worldwide, the CAM-ICU is the best validated and most frequently used delirium assessment instrument in ICU patients by non-psychiatrists.

The effects of implementation of the CAM-ICU on the treatment of delirium are unknown. It appears plausible that if a delirium assessment tool is implemented in daily practice, more delirious patients will be recognized which consequently affects the delirium treatment but this needs to be studied.

In daily clinical practice the attending ICU nurses, not research nurses, use the CAM-ICU to screen their patient. The sensitivity and specificity of the CAM-ICU when executed by the attending nurse compared with the 'gold standard' is currently unknown and is examined in this thesis.

A disadvantage of the CAM-ICU is that it is a momentary test executed only once to 3 times a day. Because of the fluctuating course of delirium, this can lead to a false negative result. If the nurse or physician suspects delirium, the patient should be tested more frequently. Although there is no evidence for the optimal number of times a day patients should be screened, it is unlikely that assessing patients only once a day would be sufficient.

Given this drawback of momentary tests it would be interesting to explore other possibilities to diagnose delirium. For many diseases specific laboratory tests are available to aid the diagnosis. Currently, no laboratory test is available to diagnose the disorder delirium. We therefore investigated the possibility to find a fingerprint for delirium using proteomics techniques.

Impact of Delirium in Intensive Care Patients

The occurrence of delirium is associated with serious health problems. Independent of age and severity of illness (14), delirious patients have a longer duration of mechanical ventilation, ICU stay, and in-hospital stay than non-delirious patients (13;15). It is unknown whether these short-term consequences are similar in all patient categories and if there are differences between the delirium subtypes.

Patients suffering from delirium have a significantly higher mortality rate than patients without delirium and delirium is reported as an independent predictor of mortality (16). Observational data show that each day a delirium continues, the risk of persisting cognitive disorders and death increases with approximately 10% (13). Although there are several long-term health related quality of life (HRQoL) studies performed in ICU patients (17-19), little is known about the effects of delirium on long-term quality of life. Therefore we explored the effect of delirium on long-term health related quality of life and on cognitive functions.

Prediction and Prevention of Delirium in Intensive Care Patients

In view of the impact of delirium there is a clear need for prevention, as well as for effective treatment. Prevention can play an important role in reducing the incidence of delirium, in addition to reducing the subsequent harm of delirium in ICU patients. Prevention of delirium is likely most efficient and effective in ICU patients with the highest risk for developing delirium. To determine which patients have a high risk for delirium a prediction model would be necessary. Such a delirium prediction model is available for hospitalized patients (20), but a delirium prediction model for ICU patients is currently lacking.

If we had a prediction model that would allow us to identify high risk patients, which preventive measures should be taken? There is some evidence that preventive measures can be effective (21;22). A multicomponent prevention

strategy was effective in reducing the delirium incidence and duration (21) and a low dose of prophylactic haloperidol resulted in a decrease in severity and duration of delirium and shortened the length of stay in-hospital (22). However, the two studies indicating this were performed in hospitalized elderly patients and not in ICU patients. Interestingly, in a retrospective cohort study a lower hospital mortality rate was found in mechanically ventilated ICU patients who received haloperidol compared with patients who were not treated with haloperidol (23), thus suggesting haloperidol may protect ICU patients in some way. Nevertheless, to date no delirium prevention studies have been performed in ICU patients. Therefore, in this thesis we describe the development and validation of a delirium prediction model for ICU patients and the effect of prophylactic use of haloperidol in ICU patients with a high risk for delirium.

Role of Biomarkers in Delirium in Intensive Care Patients

Finally, the aetiology of delirium is far from clear. A large diversity of factors are related to delirium and the pathogenesis of delirium is likely to be multifactorial (24-26). Several pathways may contribute to the development of delirium (25;27;28), the most important being the cholinergic, the serotonergic and the inflammatory pathway. The cholinergic pathway, with acetylcholine as its neurotransmitter, plays a role in consciousness and activation of cholinergic neurons is associated with dreaming, hallucinations (29) and delirium (28). The serotonergic pathway with serotonin as the principal neurotransmitter modulates mood, wakefulness and cognition (30). The inflammatory pathway also plays a role in the onset of delirium. For example, administration of the cytokine interleukin-2 results in delirium (31;32). More recently it was shown that several other proinflammatory cytokines are associated with the onset of delirium in elderly patients (27). The inflammatory pathway may even be more important in critically ill intensive care patients, since these patients suffer from more systemic inflammation than non-ICU patients.

One can hypothesize that the end-products of these different pathways exert direct injurious effects to the cells of the central nerve system and that these toxic effects can be detected through increased levels of brain specific proteins. To date, no studies are performed in which elevated levels of brain specific proteins are related to delirium. Also the role of inflammation in delirium in ICU patients is not investigated yet. In this thesis we determined the effect of several pro- and anti-inflammatory cytokines on brain function and cognition in healthy volunteers. In addition, we determined the role of these cytokines and the role of brain specific proteins in delirious ICU patients with and without evidence of an infection.

In summary, the aims of this thesis are:

- To gain more insight into the diagnosis of delirium in ICU patients using the confusion assessment tool and to explore if delirium can be diagnosed with other tools apart from the existing delirium assessment tools;
- To determine the impact of delirium on several short- and long-term health related consequences;
- To determine if delirium in ICU patients can be predicted and prevented;
- To explore the role of biomarkers in delirium in ICU patients.

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Outline of this thesis

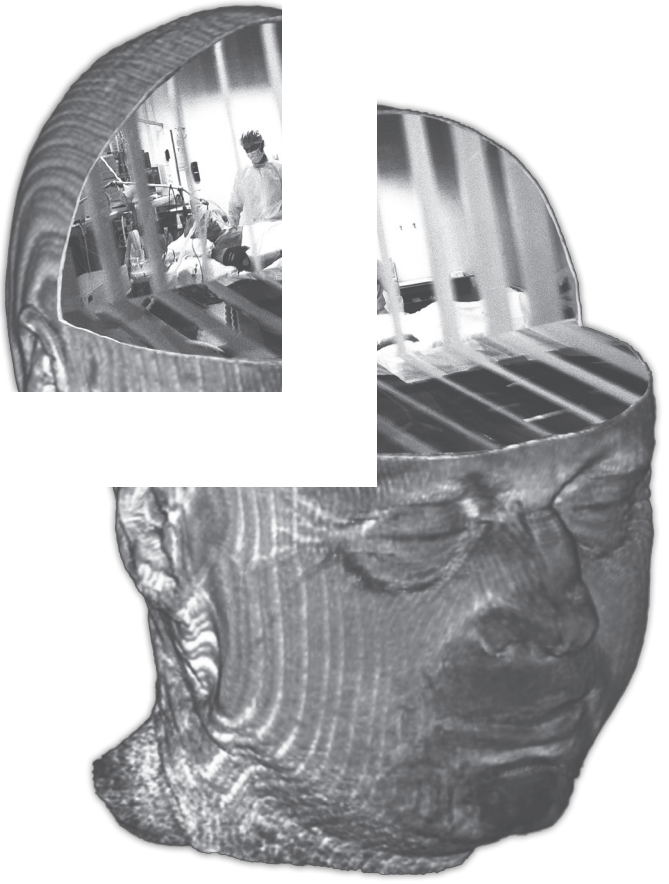
This thesis consists of four parts. **PART ONE** is focussed on the *Detection of Delirium in Intensive Care Patients*. In **Chapter 2** we describe a tailored implementation strategy, which was used to implement the validated confusion assessment method for ICU (CAM-ICU) patients. We evaluated this implementation strategy on several outcome measures and we studied the effect on the treatment of delirious patients. In the original studies of the CAM-ICU, the assessment tool had a high sensitivity and specificity when used by dedicated research nurses. In a multicentre study in the Netherlands (**Chapter 3**) we determined the performance of the CAM-ICU when used by ICU-nurses in daily practice. In **Chapter 4** we describe a prospective study in which we explored the possibility to find a fingerprint of delirium markers in the urine of patients following cardiac surgery using urinary proteomics.

In **PART TWO** we determined the *Impact of Delirium in Intensive Care Patients*. First, we focused on the delirium incidence in several admission categories of intensive care patients and short-term consequences of delirium such as duration of mechanical ventilation, unplanned removal of tubes and catheters, length of stay in the ICU and hospital (**Chapter 5**). In this study we also determined to what extent delirium contributes to these short-term consequences. Knowing that delirium is a significant predictor for mortality, in **Chapter 6** we examined if adding delirium as an additional variable to the acute physiology and chronic health evaluation (APACHE-II) score would improve the predictive estimate of the model. **Chapter 7** describes the impact of delirium on long-term health related quality of life and cognitive functioning of ICU survivors.

PART THREE focuses on the *Prediction and Prevention of Delirium in Intensive Care Patients*. In **Chapter 8** we examined the possibility to develop a delirium prediction model for ICU patients with predictors which are readily available within 24 hours after ICU admission to enable identification of high risk patients. When it would be possible to develop and to validate such a delirium prediction model it would be of interest to implement this model in daily practice and to consequently examine the effects of preventive measures taken in patients with a high risk for delirium. The effects of preventive treatment with a low dose haloperidol were examined in high risk patients in **Chapter 9**.

The last part of this thesis, **PART FOUR**, examined the *Role of Biomarkers related to Delirium in Intensive Care Patients*. We explored the role of several pro- and anti-inflammatory cytokines on brain function (measured by EEG), cognitive functioning and brain specific proteins in an experimental human endotoxemia model (**Chapter 10**). In **Chapter 11** associations of various markers of inflammation and brain specific proteins with delirium in patients with or without infection/SIRS criteria and their relation to long-term cognitive function are described.

In the general discussion, conclusions and future directives in **Chapter 12** the results described in this thesis are summarized and our findings are discussed in view of several methodological issues, clinical consequences and aims for future research.



PART ONE

Detection of Delirium in Intensive Care Patients

2

Implementation of a delirium assessment tool in the ICU can influence haloperidol use

Mark van den Boogaard, Peter Pickkers, Hans van der Hoeven, Gabriel Roodbol, Theo van Achterberg, Lisette Schoonhoven

Critical Care 2009; 13(4): R131

Abstract

Introduction

In critically ill patients, delirium is a serious and frequent disorder that is associated with a prolonged intensive care and hospital stay and an increased morbidity and mortality. Without the use of a delirium screening instrument, delirium is often missed by ICU nurses and physicians. The effects of implementation of a screening method on haloperidol use is not known. The purpose of this study was to evaluate the implementation of the confusion assessment method-ICU (CAM-ICU) and the effect of its use on frequency and duration of haloperidol use.

Methods

We used a tailored implementation strategy focused on potential barriers. We measured CAM-ICU compliance, interrater reliability, and delirium knowledge, and compared the haloperidol use, as a proxy for delirium incidence, before and after the implementation of the CAM-ICU.

Results

Compliance and delirium knowledge increased from 77% to 92% and from 6.2 to 7.4, respectively (both, p <.0001). The interrater reliability increased from 0.78 to 0.89. More patients were treated with haloperidol (9.9% to 14.8%, p < .001), however with a lower dose (18 to 6 mg, p = 0.01) and for a shorter time period (5 [IQR:2-9] to 3 [IQR:1-5] days, p = .02).

Conclusions

With a tailored implementation strategy, a delirium assessment tool was successfully introduced in the ICU with the main goals achieved within four months. Early detection of delirium in critically ill patients increases the number of patients that receive treatment with haloperidol, however with a lower dose and for a shorter time period.

Introduction

Delirium is a common psychiatric disorder in critically ill patients. It has an acute onset and combines cognitive and attention defects with a fluctuating consciousness (1). It is associated with a prolonged intensive care and hospital stay and an increased morbidity and mortality (2-4)

Although there has been increasing interest in delirium in the past five years, standard screening of patients in daily practice is still not common, resulting in an underestimation of the problem. Previous studies showed that, without the use of a screening instrument, more than 60% of patients with delirium are missed by ICU nurses and more than 70% by physicians (5;6). It can therefore be assumed that delirious patients are not sufficiently treated if they are not recognized. The incidence rate in critically ill patients varies between 11% and 87%, depending on the study design, methods for assessment, and differences in population (2;4;7-9).

Although there is no evidence that the use of a delirium assessment tool results in improvement of outcome, early recognition of delirium is important for adequate and early treatment. Therefore routine screening of patients is necessary. In addition, because of the fluctuating clinical signs and symptoms of delirium, screening should be performed at least once every 8 to 12 hours (10;11). A delirium assessment tool should therefore be quick and easy to use with a high interrater reliability.

The Dutch guidelines *Delirium in the Intensive Care* recommends the screening of all ICU patients with a reliable and validated delirium screening instrument (van Eijk MJJ, Spronk PE, van den Boogaard MHWA, Kuiper MA, Smit EGM, Slooter AJC. Delirium op de Intensive Care, unpublished data), such as the intensive care delirium screening checklist (ICDSC) (12) or the confusion assessment method-ICU (CAM-ICU) (13).

The treatment of delirium is based on removing the underlying somatic disorder frequently combined with pharmacological therapy. Although there is no clear evidence that treatment improves the prognosis of delirious ICU patients (14), and haloperidol has significant side effects (15;16), haloperidol is the most commonly recommended pharmacological agent (17). As screening will probably increase the number of patients diagnosed with delirium, it could also increase the use of haloperidol. In view of this, it is important to determine the effect of the implementation of a screening instrument on the use of haloperidol.

The first aim of our study was to evaluate our strategy for the implementation of the CAM-ICU. Therefore, the compliance with scoring of the CAM-ICU, the interrater reliability, and improvement in delirium knowledge of the nurses were used as indicators for successful implementation. We assumed that a larger number of delirious patients would be detected with the use of the CAM-ICU, in comparison

with previous periods without the standard use of a screening tool. The second aim of our study was therefore to assess how the CAM-ICU influences the frequency and duration of haloperidol use, which may be considered to be a proxy for the delirium incidence and duration.

Material and methods

This study was conducted in the Radboud University Nijmegen Medical Centre, the Netherlands, a 960-bed university hospital that includes a level 3 (highest level) ICU with 40 beds divided over four adult wards and one paediatric ward. Annually 2000 to 2500 (cardiothoracic surgery, neurosurgical, medical, surgical, and trauma) patients are admitted.

The local Institutional Review Board of Arnhem-Nijmegen indicated that for this study no approval was required and no informed consent from patients was needed.

Nurses and the implementation of the CAM-ICU

Although the ICDSC and the CAM-ICU are suitable delirium screening instruments, we preferred to implement the CAM-ICU above the ICDSC because of the higher sensitivity and specificity, and because the CAM-ICU is translated and validated in Dutch (18). The CAM-ICU is an easy to perform assessment tool for ICU nurses, which consists of a two-step approach model (13) [see Additional data file 1]. Before the implementation of the CAM-ICU, identification of delirious patients was based on the judgement of the attending ICU physician, and a delirium screening instrument was not used. Due to the potential importance of unrecognised delirium, we decided that this should be changed to a situation where regular and systematic assessment of delirium was performed by ICU nurses with specific knowledge of delirium recognition. Therefore, we introduced the CAM-ICU as an instrument for early recognition of delirium and started with the implementation on all four adult ICU wards in December 2007.

Implementation of a delirium assessment tool in daily practice introduces an essential change for ICU nurses. As there is no single best method for implementing an innovation in all settings (19), it is important to identify potential barriers and facilitators in this particular setting. For a good adaptation of a delirium screening instrument it is important to tailor the implementation strategy to these facilitators and barriers (20). Furthermore, support from the organisation and medical and nursing staff participation is important for a successful implementation (21).

Our implementation strategy [see Additional data file 2] was focused on potential barriers and facilitators for screening with the CAM-ICU (Table 1), which were

identified during several, unstructured, interviews with the nursing and medical staff.

Table 1 **Identified potential barriers and facilitators during interviews**

Implementation barriers	Implementation facilitators
1. Lack of knowledge concerning delirium	1. Patient data management system
2. Inavailability of the assessment tool	2. Senior nurses
3. To fill in the delirium assessment tool on paper three times a day ('paperwork')	3. Support of medical and nursing staff
4. Time to perform the assessment	4. Delirium researcher

We integrated the CAM-ICU algorithm in our patient data management system, which is available at all bedside computers. Because of the fluctuating course of delirium every patient had to be assessed minimally once in every eight-hour shift, according to the CAM-ICU manual (22;22). If the mental status changed after an assessment, an additional assessment had to be performed. Patients were excluded from screening when they had a Richmond agitation sedation score (RASS) of –4 or -5 (13), were unable to understand Dutch, were severely mentally disabled, or suffered from a serious receptive aphasia. All necessary testing tools (attention screening pictures and disorganized thinking questions) were made available at every bed. The computer notified the nurse about the outcome of the CAM-ICU screening, that is, delirious or not.Evidence-based interventions (23) included in the implementation strategy were: education; educational outreach visits; reminders and feedback; and leadership. Education and educational outreach visits

All ICU nurses were trained in the use of the CAM-ICU and performed a knowledge test prior to the training. The education consisted of a one-hour group training prior to the implementation of the CAM-ICU. During this training, information about delirium features, recognition, and delirium types was given. Furthermore, specific information was given about the CAM-ICU. We used educational material from the delirium website (22) such as the training video and the Harvard CAM-ICU flow sheet. We appointed 'delirium key-nurses', who received supplementary training, for further instruction and introduction of the CAM-ICU in their unit. In addition, posters with the Harvard CAM-ICU flow sheet were distributed to nurses and the medical staff. Also, the medical staff was informed about delirium and the CAM-ICU. Supplementary individual training on the job (by MvdB, and the 'delirium key-nurses') started one month after the implementation and was given whenever

screening compliance and interrater reliability dropped below the stated aim. The focus during this training on the job was on the most common mismatches, that is feature 1A and 1B [see Additional data file 1]. Determination of the presence of cognitive function disturbances and the fluctuating nature of consciousness were the most difficult points for the ICU nurses. Individual problems with the assessment were addressed by focusing the training on the difficulties experienced during observations.

Reminders and feedback

When a delirium assessment was not carried out, a pop-up appeared on the bedside computer as a reminder for the nurse. The CAM-ICU scoring rate, that is the screening compliance, and the interrater reliability were measured. The results were evaluated with the delirium key-nurses and the nursing staff, twice a week as parameters of a successful implementation. Feedback about results and performance of the CAM-ICU was supplied weekly by e-mail and during monthly clinical meetings.

Leadership

The medical and nursing staff committed themselves to, and supported the implementation of the delirium assessment tool, as agreed upon during the information meeting and was reported during feedback of the key nurses. One project leader was responsible and supervised the implementation process (MvdB). Prior to the implementation, the CAM-ICU was introduced to the medical staff. Two months after the implementation, the presence of delirium became a standard part of the daily multidisciplinary meeting, in which all patients are discussed. All ICU wards were visited daily by the project leader to identify problems concerning the performance and compliance of the assessment tool and for personal or group feedback.

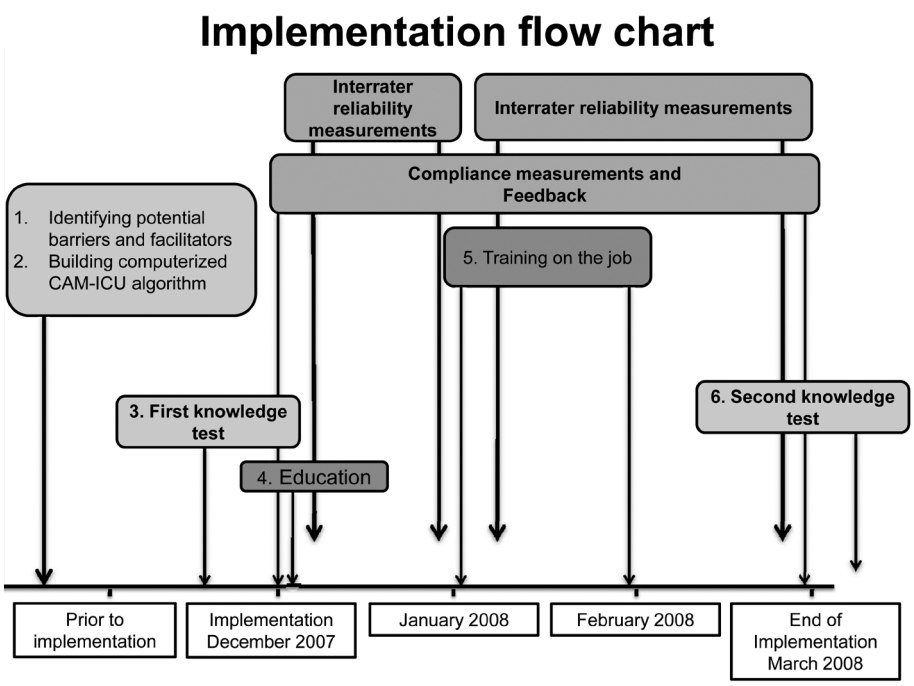
Chosen indicators of a successful implementation were: regular assessment of all ICU patients defined as a screening compliance of more than 80%; interrater reliability score of more than 0.80; and improvement of the level of knowledge concerning delirium.

The compliance was calculated as the percentage of performed assessments per day of the total number of assessments that should have been performed. Interrater reliability tests were performed several times during the first month after the implementation and twice a week during and after the training on the job period. For this the CAM-ICU score assessed by the ICU nurse was compared with the CAM-ICU score assessed by an expert psychiatric nurse (GR). The maximum period between the two assessments was one hour and patients were chosen randomly. Patients who were excluded from screening with the CAM-ICU were

also excluded from the interrater reliability testing. We developed a non-validated written delirium knowledge test that had to be completed in 10 minutes prior to the delirium training and consisted of 10 mixed open and closed questions. A similar post-training test was performed four months later. 'Delirium knowledge' is expressed on a scale of 0 to 10. The implementation period started in December 2007 and ended in March 2008, after reaching the indicators of care improvement (Figure 1). The nursing staff consists of 140 nurses of which 18 (13%) were ICU nurses in training. The patients and haloperidol treatment

As delirium incidence rates before the use of the assessment tool were not available, we used the frequency of haloperidol use as a proxy for delirium incidence. Data of all patients who were treated with haloperidol are available through our patient data management system. As a general rule, in our ICU all patients diagnosed with delirium are treated with haloperidol and delirium is the only reason for prescribing haloperidol.

Figure 1 **Implementation flow chart**



The duration of haloperidol treatment was used as a proxy for the duration of the delirious period. For the incidence rate of a four-month period (March until June 2008) after the implementation, the CAM-ICU results were compared with the haloperidol use during the same period of the two previous years. We compared

the total number of all consecutive patients treated with haloperidol, total days of treatment, and the total dose of administered haloperidol per patient and per day.

Statistical analyses

All data analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data (demographic data, knowledge level, and the scorings rate) were tested parametrically (Student's t-test, repeated measurement analysis of variance). Data concerning the treatment with haloperidol were not normally distributed and were tested non-parametrically with the Friedman test and the Kruskal-Wallis one-way analysis of variance test. Interrater reliability of the outcome of screening, that is delirious or non-delirious, was calculated with the Cohen's Kappa statistic.

Results

Evaluation of implementation and nurses

In the first month of the implementation period the interrater reliability was 0.78 (n = 25, 95% confidence interval (CI): 0.5 to 1.0) and following intensive training on the job of almost all ICU nurses this increased to 0.89 (n = 47, 95% CI: 0.75 to 1.0).

In the first month after the implementation the compliance of screening with the CAM-ICU was 77% and increased significantly to 92% (repeated measurement analysis of variance, p <.0001) after four months. Scoring rate of the nurses at the pre-course delirium knowledge test was 6.2 ± 1.7 (n = 136) and increased significantly to 7.4 ± 1.2 (n = 122) four months later (Student's t-test, p = .0001).

Haloperidol treatment and patients

With the exception of a small, but statistically significant difference in the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, the demographic variables of the patients did not differ between the three years (Table 2). In the same period in 2006 and 2007, 13 (10%) and 20 (13%) patients per month were treated with haloperidol, respectively (Table 3). Following the implementation period, based on the CAM-ICU results, this increased significantly to 37 (23%) patients per month (p <.001) compared with the previous period without the use of the CAM-ICU. All patients who received haloperidol in the period after the implementation in 2008 were detected with the CAM-ICU as delirious patients.

From these 147 delirious patients, 25 (17%) had a hyperactive type, 47 (32%) a hypoactive type, and 74 patients (50.3%) had a mixed-type delirium. During this period 641 patients were admitted of which 74 patients were excluded from CAM-

ICU screening. The most frequent reason was sustained coma (49%). To compare the effect on the detected incidence before and after the implementation of the CAM-ICU, we used the total of 641 patients, because of the lack of information of the patients in the period before the implementation.

Table 2 **Demographic variables of ICU-patients before and after implementation of CAM-ICU**

Period	Prior to implementation March to June 2006	Prior to implementation March to June 2007	After implementation March to June 2008	*p* value
Number of patients	512	589	641	
Age	57.5 ± 16.4	58.9 ± 16.6	59.5 ± 15.6	*N.S.*
Gender (M/F)	339/173	370/219	409/232	*N.S.*
APACHE-II score	16.9 ± 7.0	17.1 ± 6.9	15.5 ± 6.5	*.0001*
Length of stay on ICU in days (median (IQR))	1.3 (0.8 to 5.9)	1.0 (1 to 5)	1.0 (1 to 3)	*N.S.*
Admission type (n)				
Elective surgery	214 (42%)	283 (48%)	340 (53%)	*N.S.*
Urgent surgery	106 (20%)	96 (16%)	76 (12%)	
Medical	192 (38%)	210 (36%)	225 (35%)	

All values are means ± standard deviation unless otherwise reported.
APACHE II = Acute Physiology and Chronic Health Evaluation II; CAM-ICU = confusion assessment method-intensive care unit; F = female; ICU = intensive care unit; IQR = interquartile range; M= male; N.S. = non-significant.

The median duration of treatment with haloperidol decreased from five (interquartile range (IQR) 2 to 9) to three days (IQR 1 to 5) after the implementation of the CAM-ICU (p = .02). The median total haloperidol dose per patient (during treatment) decreased from 18 mg (IQR 5 to 39.5) to 6 mg (IQR 2 to 19.5; p = .01).

Table 3 **Effect of the implementation of the CAM-ICU in 2008 on delirium treatment**

	2006 (n = 512)	2007 (n = 589)	2008 (n = 641)	*p* value
Total numbers of delirious patients (%)	51 (10%)	79 (13%)	147 (23%)	*< .0001*
Number of delirious patients per month	13	20	37	*< .0001*
Total dose of haloperidol per patient (mg)	18 (5 to 40)	12.5 (3 to 30)	6 (2 to 20)	*.01*
n = total number of patients treated with haloperidol	(n = 52)	(n = 80)	(n = 147)	
Duration of treatment (days)	5 (2 to 9)	3 (2 to 9)	3 (1 to 5)	*.02*

All values are medians (interquartile range) unless other reported. CAM-ICU = confusion assessment method-intensive care unit.

Discussion

In a relatively short period of four months, we successfully implemented a validated delirium assessment tool in our daily practice on the ICU. Following the implementation of the CAM-ICU, more patients were treated with haloperidol, but with a lower dose and for a shorter period of time when compared with the same period in the two previous years. Almost two times more delirious patients were detected with the use of the CAM-ICU. Our results indicate that successful implementation of the CAM-ICU is possible and, importantly, that this results in shorter and lower dosed haloperidol treatment.

The implementation of the CAM-ICU

We feel that several aspects of our implementation strategy are responsible for this success. First, we used a multifaceted model with evidence-based interventions. Although we did not measure the effect of the separate interventions, previous studies showed that education and feedback with reminders are very effective interventions (23). Second, it is important to focus the implementation strategy on potential barriers that can be expected in daily practice (19), which will differ from hospital to hospital and from ward to ward. We therefore gathered information about these potential barriers prior to the actual implementation. Based on this information, we used the facilitators of our organization and integrated the CAM-ICU in our patient data management system. Although it took some time to develop the integrated CAM-ICU, it was easier to use and included a reminder when the assessment had not been performed at the end of the shift. The key-nurses played an important role in supporting the group and therefore were pivotal. They were

also particularly helpful in bedside training of the ICU nurses, their direct colleagues.

A final point of interest is the cooperation with the medical staff. We noticed that it is important that the CAM-ICU score is part of the daily evaluation of the patient and that it is also important to react adequately to a positive delirious score by treating the patient. Therefore, it is also important to inform the medical staff during the implementation (education) and give them regular feedback on the results of the implementation (compliance, interrater reliability, and delirium knowledge level). As these interventions are tailored to the barriers found in this study they should not be used as a blueprint for implementation but could serve as a guideline.

Although the CAM-ICU appears to be relatively simple to use and a relatively short training period should result in a reliable performance of the CAM-ICU (11;13), our study demonstrates that an intensive implementation strategy results in a further improvement of its performance. We aimed for a group interrater reliability score of at least 0.8, which can be considered a desirable (24) and attainable goal for the CAM-ICU (13). Evidently, it is of utmost importance to test the reliability of the assessment by the ICU nurses, because a false-positive diagnosis may result in unnecessary treatment and vice versa. Therefore, in our view, it is necessary to perform interrater reliability tests and analyse the mismatches to be able to give adequate feedback. Unfortunately, and surprisingly, not much attention is given to this aspect in the literature and many new screening and treatment policies appear to be implemented without it.

Although a high interrater reliability is important for the performance of the CAM-ICU, a screening tool will only be effective when the compliance with its use is also high. Although we did not formally measure the nursing workload, it is clear that the screening of patients with the CAM-ICU results in some additional work for the nurses. Our experience is that the mean screening time of the patients with the CAM-ICU is two to five minutes, which is comparable with that mentioned by Ely and colleagues (13). Based on a study by Soja and colleagues (25) we chose an 80% compliance with the CAM-ICU as a feasible and acceptable aim for a successful implementation. Scoring all patients three times a day during their whole stay on the ICU is hardly realistic. Moreover, an optimal compliance is unknown. We are convinced that the intensive feedback and support of the project leader and the medical and nursing staff played an important role in achieving a high compliance.

Haloperidol treatment and patients

One could argue that haloperidol use is not a good proxy for the incidence of delirium because it is also used to treat other disorders such as serious psychoses, severe excitement, and anxiety (26). However, these disorders are rarely observed in our ICU or not treated with haloperidol. In the case of agitation in patients without

a protected airway we use a low dose of propofol, if necessary in combination with oxazepam. Therefore we are confident that in our ICU only delirious patients are treated with haloperidol and that the observed difference in haloperidol use between the compared treatment periods can only be attributed to differences in delirium detection rate.

Despite the fact that we found a higher incidence of delirious patients with the CAM-ICU than without the use of a screening instrument, the incidence in our population is low. A possible explanation is that the study was performed in all consecutive patients, with no selection of high-risk patient groups. Including patients that were admitted to our ICU following elective surgery may also partly explain why the APACHE II score is lower compared with other studies that reported higher APACHE II scores associated with a higher incidence of delirium (13;27;28).

It is assumed that the regular use of a delirium assessment tool results in a higher detection rate of delirious patients, especially patients with a hypoactive delirium. Naturally, this could result in more haloperidol use. Given the potential side effects of the drug, the absence of clear evidence that presence of hypoactive delirium is associated with poor patient outcome and that the use of a delirium assessment tool improves the outcome of the ICU patient, one might argue that an increase in haloperidol use is not desirable. On the other hand, an earlier and improved recognition of delirious patients may make it easier to treat the delirium with lower doses of haloperidol. To our knowledge, the influence of performing the CAM-ICU on the total amount of haloperidol used per patient has not been studied before. It appears plausible that, besides the earlier detection of delirious patients, also recovery from the delirious period could be detected earlier with the use of a delirium assessment tool. As a result, haloperidol treatment would be stopped earlier. Our data confirm these assumptions. It is also possible that the early treatment of delirium could result in shortening of the delirious period, but this assumption needs further study.

Conclusions

Tailoring our implementation strategy to the needs of the ICU was successful. The main goals were achieved within a relatively short time. Early recognition of delirium with the CAM-ICU has become a standard component of daily care by the nurses in our ICU and contributes to the quality of care. In addition, early detection of delirium leads to lower dosage and shorter periods of haloperidol treatment in critically ill patients.

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Appendix 1 CAM-ICU worksheet

Feature 1: Acute Onset or Fluctuating Course Positive if answer ' yes' to either 1A or 1B	Positive	Negative
1A: Is the pt. different than his/her baseline mental status? Or **1B**: Has the patient had any fluctuation in mental status in the past 24 hours as evidence by fluctuation on a sedation scale (e.g. RASS) GCS, or previous delirium assessment	Yes	No
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. Attempt the ASE letters first. If pt. Is able to perform this test and the score is clear, record this score and move to Feature 3. If pt. Is unable to perform this test or the test score is unclear, then perform the ASE pictures. If you perform both tests, use the ASE pictures' results to score the Feature	Positive	Negative
2A: ASE letters: record score (enter NT for not tested) *Directions: Say to the patient, "I am going to read you a series of 10 letters. When you hear the letter 'A' indicate by squeezing my hand". Read letters from the following letter list in a normal tone.* SAVEAHAART Scoring: errors are counted when patient fails to squeeze on the letter 'A' and when the patient squeezes on any letter other than 'A'.	Score (out of 10):----------	
2B: ASE pictures: record score (enter NT when not tested) *Directions are included on the picture packets.*	Score (out of 10):----------	
Feature 3: Disorganized thinking Positive if the combined score is less than 4	Positive	Negative
3A: Yes/No Questions (Use either Set A or B, alternate on consecutive days if necessary): **Set A** / **Set B** 1. Will a stone float on water? / 1. Will a leaf float on water? 2. Are there fish in the sea? / 2. Are there elephants in the sea? 3. Does one pound weigh more than two pounds? / 3. Do two pounds weight more than one pound? 4. Can you use a hammer to pound a nail? / 4. Can you use a hammer to cut wood? **Score_____**(patient earns 1 point for each correct answer out of 4) **3B:** Command Say to patient: "Hold up this many fingers"(examiner holds two fingers in front of patient) "Now do the same thing with the other hand"(not repeating the number of fingers). *If pt. Is unable to move both arms, for the second part of the command ask patient "Add one more finger") **Score_____**(Patient earns 1 point if able to successfully complete the entire command)	Combined Score (3A=3B): _____ (out of 5)	
Feature 4: Altered level of consciousness Positive if the actual RASS score is anything other than "0" (zero)	Positive	Negative
Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Positive	Negative

With permission of the authors.

Appendix 2 Textbox: Implementation strategy

Interventions for the CAM-ICU implementation. We:

1. made an inventory of potential facilitators and barriers of our organization
2. tailored the implementation strategy to the potential barriers and opportunities
3. set clear and feasible targets for a successful implementation
4. computerized the CAM-ICU algorithm in our system and made it user friendly
5. integrated reminders for screening in the computerized CAM-ICU
6. equipped every bed with all necessary tools for the assessment performance
7. appointed delirium 'key-nurses' for dissemination of delirium knowledge and assistance during the implementation
8. involved medical and nursing staff in the implementation
9. performed interrater reliability tests and provided extra training on the job on

3

Routine Use of the Confusion Assessment Method for the Intensive Care Unit: A Multicenter Study

Maarten M. van Eijk, Mark van den Boogaard,
Rob J. van Marum, Paul Benner, Piet Eikelenboom,
Marina L. Honing, Ben van der Hoven, Janneke Horn,
Gerbrand J. Izaks, Annette Kalf, Attila Karakus, Ine A. Klijn,
Michael A. Kuiper, Frank-Erik de Leeuw, Tjarda de Man,
Roos C. van der Mast, Robert-Jan Osse, Sophia E. de Rooij,
Peter E. Spronk, Peter H. van der Voort, Willem A. van Gool,
Arjen J. Slooter

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Abstract

Rationale

Delirium is often unrecognized in Intensive Care Unit (ICU) patients and associated with poor outcome. Screening for ICU delirium is recommended by several medical organizations to improve early diagnosis and treatment. The Confusion Assessment Method for the ICU (CAM-ICU) has high sensitivity and specificity for delirium when administered by research nurses. However, test characteristics of the CAM-ICU as performed in routine practice are unclear.

Objective

To investigate the diagnostic value of the CAM-ICU in daily practice.

Methods

Teams of three delirium experts including psychiatrists, geriatricians and neurologists visited ten ICUs twice. Based on cognitive examination, inspection of medical files and DSM-IV-TR criteria for delirium, the expert teams classified patients as awake and not delirious, delirious or comatose. This served as gold standard to which the CAM-ICU as performed by the bedside ICU-nurses was compared. Assessors were unaware of each-others conclusions.

Main results

Fifteen delirium experts assessed 282 patients of whom 101 (36%) were comatose and excluded. In the remaining 181 (64%) patients, the CAM-ICU had a sensitivity of 47% (95% Confidence Interval (CI) 35% - 58%), specificity of 98% (95% CI 93% - 100%), positive predictive value of 95% (95% CI 80% - 99%) and negative predictive value of 72% (95% CI 64% - 79%). The positive likelihood ratio was 24.7 (95% CI 6.1-100) and the negative likelihood ratio 0.5 (95% CI 0.4-0.8).

Conclusions

Specificity of the CAM-ICU as performed in routine practice appears to be high but sensitivity low. This hampers early detection of delirium by the CAM-ICU.

Introduction

Delirium is characterized by an acute disturbance of consciousness and attention with cognitive or perceptual changes and often a fluctuating course (1). It is common in Intensive Care Unit (ICU) patients, with an incidence during ICU stay ranging up to 89% (2-8). In ICU patients, delirium is associated with poor outcome, including increased mortality, increased ICU and hospital length of stay, more cognitive impairment after hospital discharge and higher health-care related costs (4;9-11).

Despite its frequency and impact, delirium in the ICU goes often unrecognized which hampers early treatment (12). The clinical impression of ICU physicians and nurses whether or not an ICU patient was delirious had a sensitivity of 29% and 35% respectively, compared to the conclusion of delirium experts (13;14). To improve early recognition of delirium, several easy-to-use screening methods have been developed (15), such as the Confusion Assessment Method adopted for the Intensive Care Unit (CAM-ICU)(16) and the Intensive Care Delirium Screening Checklist (ICDSC) (17). Of these, the CAM-ICU had higher sensitivity (64%; specificity 88%) than the ICDSC (sensitivity 43%; specificity 95%) within the same population of mixed ICU patients (13), and is therefore the most frequently used delirium detection tool(18).

Several medical organizations, including the Society of Critical Care Medicine (SCCM) and the American Psychiatric Association (APA), advise standard screening for delirium in critically ill patients (12;19). The CAM-ICU showed high sensitivity (range 97%-100%) and specificity (range 89%-100%) in several validation studies (16;20-22). It should however be noted that all these investigation were performed in research settings (16;20-22), which may differ from day-to-day critical care (23). Test characteristics of the CAM-ICU as performed by bedside ICU nurses are unknown. The aim of this study was to investigate the diagnostic value of the CAM-ICU when performed by bedside ICU nurses in routine daily practice. Some of the results of this study have been previously reported in the form of an abstract (24-26).

Methods

Design and Setting

This prospective multicenter study was performed in ten ICUs of university, teaching and rural hospitals in the Netherlands, which were selected based on a previous nation-wide survey on the use of delirium monitoring (18). The study population consisted of mixed medical and surgical ICU patients who were admitted to one of the participating ICUs during visits of delirium experts, as described below. Patients who were unable to speak Dutch or English, and those who could not be examined due to logistic reasons were excluded. This study was approved by the institutional review board of the University Medical Center Utrecht and a waiver for informed consent was obtained.

Implementation of the CAM-ICU

Investigators in each participating center completed a questionnaire concerning the implementation of the CAM-ICU at their ICU. They registered whether lectures had been given to nurses preceding implementation in the daily routine of that specific ICU, and whether written information was provided explaining the use of the CAM-ICU. Furthermore, local investigators were asked if individual bedside training had been given to the nurses and whether the ICU physicians always or regularly used the CAM-ICU results at their daily rounds. Lastly, the local investigators registered compliance rate of the CAM-ICU in daily practice.

Delirium assessment

During visits to the participating centers, a group of three experts made rounds along all admitted ICU patients at that time. One of these experts was either a research-physician (MMJvE) or a nurse-scientist (MvdB), who guaranteed that all assessments and study-procedures were performed uniformly. The other two experts were, in different combinations guaranteeing a multidisciplinary team, psychiatrists (n=5), geriatricians (n=4) or neurologists (n=4), who had on average 16 years (standard deviation (SD) 5) clinical experience after their medical specialist registration and who saw an estimated 20 (mean; SD 8) delirious patients monthly. To guarantee blinding for CAM-ICU scores of preceding days, experts were not allowed to evaluate patients in their own center. The expert groups assessed the patients using the Diagnostic Statistic Manual, 4th edition (DSM-IV-TR) (1) criteria for delirium, based on clinical assessment for cognitive dysfunction and a review of the medical charts, but remained blinded to reported CAM-ICU scores. The group of experts classified each patient as: 1) awake and not delirious; 2) delirious or 3) comatose, i.e. not assessable due to a low level of consciousness. If they diagnosed

a patient as delirious they had to classify whether they thought the patient suffered from a hypoactive-, a hyperactive- or a mixed type of delirium. The expert groups remained blinded for the CAM-ICU as scored by the nurses throughout the visit.

The bedside nurses assessed all patients using the Dutch version of the CAM-ICU (22) within three hours of the expert assessment, without extra training for this study. We further registered the CAM-ICU scores on the day before and the day after the experts visits. The ICU nurses were blinded for the assessment by the expert groups and received no notice before the study visits were made.

Other data collection

Local investigators supplied data on age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, admitting discipline and the (in)ability to verbally communicate (e.g. intubation or tracheotomy) at the moment of assessment. The timing of the administration of psychoactive medication (for example antipsychotics, opiates or benzodiazepines) and the timing of assessment by the expert group and the bedside nurse were also noted by the local investigator.

Statistical analysis

After exclusion of patients who were non-assessable by either the expert groups or the nurses, we calculated the sensitivity, specificity, positive predictive value and negative predictive value for the CAM-ICU, based on 2x2 tables, with the classification of the expert groups as reference. Furthermore, as delirium may vary in time, we analyzed test characteristics using RASS and CAM-ICU results from the day before and the day after the experts visits, based on the following classification: 'always RASS < -3 during this 48 hours period', or 'never a positive CAM-ICU during this 48 hours period' or 'a positive CAM-ICU at one or more moments during this 48 hours period', and the reference described above. Pre-specified stratified analyses were performed on type of delirium (hypoactive-, hyperactive- or mixed type), study center and ability of verbal communication. Agreement between the CAM-ICU results and the expert groups was computed with Cohen's kappa coefficient (κ).

Results

Between April 2009 and April 2010 all 10 participating centers were attended twice. The expert groups visited 306 different patients of whom 282 (92%) were assessable as either awake and not-delirious, or delirious or comatose. We excluded 14 patients (5%) who could not speak Dutch or English. Ten patients (3%) could not be assessed because they underwent an examination or a procedure when the expert group made their round. The average age in the included patients was 59 years (SD 18) and the average APACHE II score was 18.6 (SD 7.5), see Table 1.

Table 1 Characteristics of the study population

Characteristic	Total (n=282)	Delirium* (n= 80)	No delirium* (n=106)	Coma* (n=96)
Age (years), mean (SD)	59 (18)	62 (15)	59 (16)	57 (21)
Gender, male, n (%)	172 (61 %)	54 (68%)	64 (60%)	54 (56%)
APACHE-II score, mean (SD)	18.6 (7.5)	20.1 (7.0)	16.2 (6.9)	20.2 (7.8)
Admitting discipline, n (%)				
- Internal medicine	96 (34%)	29 (36%)	37 (36%)	30 (31%)
- General surgery	90 (32%)	23 (29%)	29 (26%)	38 (40%)
- Cardiology / cardiothoracic surgery				
- Neurology / neurosurgery	62 (22%)	21 (25%)	24 (22%)	17 (17%)
	34 (12%)	7 (10%)	16 (16%)	11 (12%)
Able to communicate verbally, n (%)	107 (38%)	36 (45%)	71 (67%)	0 (0%)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; SD = Standard Deviation.

**As defined by DSM-IV-TR criteria and assessed by experts.*

The participating centers admitted on average 1545 patients a year (SD 500) and had, on average, 25 beds (SD 12) all with capability for mechanical ventilation (see Table 2). All ICUs worked according to closed format formula with on average 9 (SD 3) intensivists. Concerning the implementation of the CAM-ICU, all participating ICUs reported to have provided lectures and written information to their nurses before its introduction. The majority of centers (60%) offered individual bedside teaching before or during the introduction of the CAM-ICU.

Table 2 Characteristics of the participating ICUs

Characteristics	Center A	Center B	Center C	Center D	Center E	Center F	Center G	Center H	Center I	Center J
Beds per center, n	33	10	32	12	10	24	50	32	30	10
Intensivists (full-time equivalents) per center, n	20	4	11	5	4	7	19	11	10	4
Annually admissions per center, n	2,250	600	2,500	640	800	1,456	1,952	2,000	2,000	713
Time from implementation CAM-ICU to participation in study, months	36	48	36	24	12	36	12	12	24	12
Lectures given	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Written information available	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Individual bedside training	Y	Y	Y	N	N	Y	N	N	Y	Y
Duration of individual training, minutes	20	30	10	N/A	N/A	20	N/A	N/A	20	10
Use of dedicated training nurses	Y	Y	N	Y	N	N	Y	N	N	N
Standard use of CAM-ICU in daily decision making	A	A	R	A	R	R	R	R	R	R
Trained nurses, %	95%	95%	80%	N/A	N/A	90%	N/A	N/A	80%	90%
Compliance to the daily CAM-ICU, %	93%	95%	90%	70%	90%	80%	95%	80%	85%	95%
Frequency of CAM-ICU per day	3	3	3	3	2	2	2	2	3	2

Definition of abbreviations: A = always; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; N = no; N/A = not applicable; R = regularly; Y = yes.

In three out of ten participating centers, CAM-ICU test results as performed by the ICU nurse, were always part of the standard evaluation by the attending intensivist. In the other centers, CAM-ICU results were regularly used. The average time from implementation of the CAM-ICU to participation in this study was two years (SD 0.5).

The expert groups reached consensus in all 282 cases, who were classified as awake and not-delirious (n=106, 38%), delirious (n=80, 28%) or comatose (n=96, 34%, Table 3).

Table 3 Overall classification of the study population

	Delirium*	No delirium*	Coma*	Total
CAM-ICU positive	35	2	7	44
CAM-ICU negative	40	104	15	159
RASS < -3	5	0	74	79
Total	80	106	96	282

*Definition of abbreviations: CAM-ICU = Confusion Assessment Method for the Intensive Care Unit administered by the bedside nurse; RASS = Richmond Agitation and Sedation score. *According to the delirium experts and DSM-IV-TR criteria.*

Of these 282 patients, 159 (56%) patients were scored CAM-ICU negative by the bedside nurses, 44 subjects (16%) as CAM-ICU positive and 79 patients (28%) as RASS (Richmond Agitation and Sedation Score) < -3 (not assessable). In total, 101 patients were identified as comatose, either by the expert groups or by the bedside nurses, and excluded to calculate sensitivity, specificity and predictive values of the CAM-ICU. The kappa score for agreement between CAM-ICU results and expert conclusions was $\kappa = 0.63$.

As shown in Table 4, delirium was detected in 75 out of 181 remaining patients by the experts. The CAM-ICU as administered by the bedside nurses was positive in 35 of these 75 subjects. This yielded an overall sensitivity of 47% (95% CI 35% - 58%) and a specificity of 98% (95% CI 93% - 100%). The overall positive and negative predictive value (PPV and NPV) were 95% (95% CI 80% - 99%) and 72% (95% CI 64% - 79%) respectively. The positive likelihood ratio was 24.7 (95% CI 6.1-100) and the negative likelihood ratio 0.5 (95% CI 0.4-0.8), see supplement Table S1. When this analysis was based on the RASS and CAM-ICU cores the day before, the day of, and the day after the expert assessment, we found the sensitivity to be 53% (95% CI 41%-65%), the specificity 86% (95% CI 77%-92%), the PPV 73% (95% CI 60% - 83%) and the NPV 72% (95% CI 64%-79%).

Table 4 Test characteristics of the confusion assessment method for the Intensive Care Unit

(Sub-) population (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Total population (n=181)	47% (35%-58%)	98% (93%-100%)	95% (80%-99%)	72% (64%-79%)
Psychoactive medication between assessments				
- Yes (n=46)	54% (33%-74%)	95% (75%-99%)	93% (64%-99%)	65% (47%-81%)
- No (n=135)	43% (30%-58%)	99% (93%-100%)	96% (76%-100%)	74% (64%-82%)
Delirium subtypes*				
- Hypoactive (delirious n=36; not delirious n=106)	31% (17%-48%)	98% (92%-99%)	85% (54%-97%)	81% (72%-87%)
- Hyperactive (delirious n=7; not delirious n=106)	100% (56%-100%)	98% (93%-100%)	78% (40%-96%)	100% (95%-100%)
- Mixed type (delirious n=32; not delirious n=106)	53% (35%-74%)	98% (93%-100%)	90% (65%-98%)	87% (80%-93%)
Admitting discipline				
- Internal medicine (n=52)	54% (33%-73%)	96% (78%-100%)	93% (64%-100%)	69% (52%-83%)
- General surgery (n=64)	38% (21%-59%)	97% (85%-100%)	91% (57%-100%)	70% (55%-81%)
- Cardiology / cardiothoracic surgery (n=43)	58% (34%-79%)	100% (83%-100%)	100% (68%-100%)	75% (56%-88%)
- Neurology / neurosurgery (n=22)	17% (1%-64%)	100% (76%-100%)	100% (1%-100%)	76% (52%-91%)
Communication ability				
- Verbal communication possible (n=109)	42% (26%-61%)	99% (91%-100%)	93% (66%-99%)	79% (68%-86%)
- Verbal communication not possible (n=72)	50% (34%-66%)	97% (82%-100%)	95% (74%-100%)	61% (46%-74%)
Center (number of included patients)				
- A (n=26)	71% (42%-90%)	92% (60%-100%)	91% (57%-100%)	73% (45%-91%)
- B (n=9)	50% (4%-91%)	100% (46%-100%)	100% (20%-100%)	71% (30%-95%)
- C (n=34)	29% (10%-58%)	100% (80%-100%)	100% (40%-100%)	67% (47%-82%)
- D (n=20)	60% (17%-93%)	93% (66%-100%)	75% (22%-99%)	88% (60%-98%)
- E (n=10)	33% (2%-87%)	100% (56%-100%)	100% (5%-100%)	78% (40%-96%)
- F (n=15)	N/A	100% (31%-100%)	N/A	20% (5%-49%)
- G (n=26)	44% (21%-69%)	100% (66%-100%)	100% (56%-100%)	53% (29%-75%)
- H (n=14)	80% (30%-99%)	100% (63%-100%	100% (40%-100%)	90% (54%-99%)
- I (n=20)	44% (15%-77%)	100% (68%-100%)	100% (39%-100%)	69% (41%-88%)
- J (n=7)	N/A	100% (46%-100%)	N/A	71% (30%-95%)

*Definitions of abbreviations: CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; CI = Confidence Interval; N/A = not applicable (no delirious patient identified); NPV = negative predictive value; PPV = positive predictive value. *according to the expert groups*

The median duration between evaluation by the expert group and assessment with the CAM-ICU was 86 minutes (interquartile range (IQR) 41-168 minutes). Based on this interval, data were divided in quartiles and analyses were repeated. No substantial differences were found between the lowest quartile (interval less than 41 minutes: sensitivity 36% (95% CI 14%-64%); specificity 100% (95% CI 86% - 100%); PPV 100% (95% CI 46%-100%) and NPV 78% (95% CI 61%-89%) and the highest quartile (interval longer than 168 minutes: sensitivity 43% (95% CI 24%-65%); specificity 95% (95% CI 74%-99%); PPV 90% (95% CI 57%-99%) and NPV 61%

(95% CI 42%-77%). In 31% of patients (n = 87) the evaluation of the experts preceded the assessment of the nurses; in 69% of patients (n = 195) the assessment of the nurses preceded the visit of the experts. When we compared test characteristics between these two groups, no substantial differences in sensitivity, specificity, PPV and NPV were found (data not shown).

All analyses were repeated after exclusion of 46 patients (25%) who had received psychoactive medication between both assessments, which did not differ from the above described overall results: sensitivity 43% (95% CI 30% - 58%); specificity 99% (95% CI 93% - 100%); PPV 96% (95% CI 76% - 100%) and NPV 74% (95% CI 64% - 82%).

After stratification according to type of delirium, sensitivity of the CAM-ICU was lowest in the hypoactive subgroup (31%; 95% CI 17% - 48%), highest in the hyperactive delirious patients (100%; 95% CI 56% - 100%) and intermediate in the mixed type patients (53%; 95% CI 35% - 74%). As further shown in Table 4, the CAM-ICU showed particularly poor test characteristics in neurocritical care patients (sensitivity 17%; 95% CI 1% - 64%). Centers always using the CAM-ICU result to adapt clinical practice on a daily base showed better test characteristics than centers in which the CAM-ICU was regularly used, especially with regard to sensitivity (range 50%-71% respectively 29%-80%).

Discussion

In summary, we found in this multicenter evaluation of daily practice, the CAM-ICU to have a sensitivity and specificity of 47% and 98% respectively and positive and negative predictive values of 95% and 72% respectively. Sensitivity was particularly poor in neurocritical care patients, in patients with hypoactive delirium and in centers where the test results were not always part of the standard evaluation by the attending intensivist. The sensitivity remained low when CAM-ICU results from a 48 hours period were considered.

The CAM-ICU in daily practice showed thus not quite as good test characteristics as presented in the original validation studies (16;20-22), where a limited number of specially trained research nurses performed the test and some categories of ICU patients were excluded (such as patients with a neurological disorder). The discrepancy in findings may also be due to inadequate training and/or by incomplete implementation of the CAM-ICU in daily routine. As training was comprehensive and did not essentially differ between centers, a possible explanation for our results may be that bedside nurses lack motivation to perform the CAM-ICU correctly if it is not standard to always evaluate the result in the treatment of their patients. However, even in centers where the test results were always part of the standard

evaluation by the intensivist, sensitivity was still substantially lower (50%-71%) than in the original validation studies (97%-100% (16;20-22)).

Strengths of this study include the sample size. This study is the largest study on this topic, with 181 included non-comatose patients from ten different ICUs. Earlier CAM-ICU validation studies (16;20-22) included less patients (range 30-129) and had all a single-center design, potentially hampering external validity. Most importantly, in all previous studies, assessments were performed by a limited number of research nurses, whereas our investigation is an evaluation of daily life. The gold standard classification was made by multidisciplinary expert groups comprising physicians from other centers with significant expertise and experience in assessing patients with delirium. Furthermore, it was ensured that the assessments and study procedures by the expert groups were always performed similarly. As the expert groups were unaware of the CAM-ICU as registered by the bedside nurses, and bedside nurses were blinded to the examinations and conclusions of the expert groups, our findings are not subject to bias.

This study has also some limitations. The classification of the type of delirium by the experts may have lacked accuracy as it was based on an assessment at a given moment in time, while delirium symptoms tend to fluctuate over the day.

Secondly, expert assessment and the CAM-ICU could not always be performed immediately after each other. As delirium tends to fluctuate during the course of the day, discrepancies between the two assessments might result from differences in clinical presentation over time. However, our results were not related to the time interval in between assessments, did not change when we excluded patients who had received psychoactive medication in between evaluations and were essentially similar when we stratified on the order of the assessments. Therefore our findings seem not to be subject to bias. Moreover, time between assessments was comparable to the original validation studies (16;20).

Thirdly, we stratified our results according to study center and related these findings to differences in training and implementation. These observations should however be interpreted with caution as the number of patients per center was small and the exact process of training and implementation was difficult to objectify.

Fourthly, a possible concern is the generalizability of our findings. The participating centers were selected from all Dutch ICU's based on a previous survey on routine delirium monitoring(18). As these centers represent the ICUs were delirium monitoring was implemented earliest, these centers most likely are the most active sites with regard to delirium care. It seems therefore unlikely that our selection of study centers has negatively influenced test characteristics of the CAM-ICU.

High sensitivity is an essential feature for a screening instrument, because screening is about to identify all patients with the disease. In our study, sensitivity

of the CAM-ICU was overall 47% and 31% for hypoactive delirium, the delirium subtype most difficult to recognize for ICU physicians (13). This low sensitivity of the CAM-ICU hampers its use as a screening instrument for delirium in critically ill patients. The specificity and the positive predictive value were however high. The higher sensitivity of the CAM-ICU found in centers always using the CAM-ICU results in daily care suggests that this may be a necessary condition for achieving adequate implementation in daily practice. Furthermore, sensitivity may be increased by combining CAM-ICU results with observations described in nursing files (27). Results from clinical efficacy trials often contradict with results from 'real-world' analyses (23). In this study we have shown that this may also apply for screening instruments.

In conclusion, in this multicenter study, specificity of the CAM-ICU as performed in daily critical care appears to be high but sensitivity low. The low sensitivity of the CAM-ICU in routine practice hampers early detection of delirium.

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Supplement

Table 1 **Likelihood ratios of the CAM-ICU**

(Sub-) population (n)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Total population (n=181)	24.7 (6.1-99.7)	0.5 (0.4-0.7)
Psychoactive medication between assessments		
- Yes (n=46)	12.0(1.7-83.8)	0.6 (0.5-0.7)
- No (n=135)	35.8 (5.0-257.6)	0.5 (0.3-0.7)
Delirium subtypes*		
- Hypoactive (delirious n=36; not delirious n=106)	16.2 (3.8-69.6)	0.7 (0.6-0.9)
- Hyperactive (delirious n=7; not delirious n=106)	53.0 (13.4-209.5)	0.0 (0.0)
- Mixed type (delirious n=32; not delirious n=106)	27.4 (6.6-112.5)	0.5 (0.3-0.7)
Admitting discipline		
- Internal medicine (n=52)	14.1 (2.0-99.7)	0.5 (0.3-0.7)
- General surgery (n=64)	14.6 (2.0-107.4)	0.6 (0.5-0.9)
- Cardiology / cardiothoracic surgery (n=43)	N/A	0.4 (0.2-0.7)
- Neurology / neurosurgery (n=22)	N/A	0.8 (0.6-1.2)
Communication ability		
- Verbal communication possible (n=109)	30.1 (4.1-219.5)	0.6 (0.4-0.8)
- Verbal communication not possible (n=72)	16.0 (2.3-112.9)	0.5 (0.4-0.7)
Center (number of included patients)		
- A (n=26)	8.6 (1.3-57.6)	0.3 (0.1-0.7)
- B (n=9)	N/A[f]	0.5 (0.2-1.3)
- C (n=34)	N/A[f]	0.7 (0.5-1.0)
- D (n=20)	9.0 (1.2-68.1)	0.4 (0.1-1.3)
- E (n=10)	N/A[f]	0.7 (0.3-1.5)
- F (n=15)	N/A[f]	1.0 (1.0-1.0)
- G (n=26)	N/A[f]	0.6 (0.4-0.9)
- H (n=14)	N/A[f]	0.2 (0.0-1.2)
- I (n=20)	N/A[f]	0.6 (0.3-1.0)
- J (n=7)	N/A[f]	1.0 (1.0-1.0)

*Definition of abbreviations: CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; N/A = not applicable (no false positive CAM-ICU result). * according to the expert groups.*

4

Urinary protein profiling in hyperactive delirium and non-delirium cardiac surgery ICU patients

Mark van den Boogaard, Rachel P.L. van Swelm,
Frans G.M. Russel, Suzanne Heemskerk,
Johannes G. van der Hoeven, Rosalinde Masereeuw,
Peter Pickkers

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Abstract

Background

Suitable biomarkers associated with the development of delirium are still not known. Urinary proteomics has successfully been applied to identify novel biomarkers associated with various disease states, but its value has not been investigated in delirium patients.

Results

In a prospective explorative study hyperactive delirium patients after cardiac surgery were included for urinary proteomic analyses. Delirium patients were matched with nondelirium patients after cardiac surgery on age, gender, severity of illness score, LOS-ICU, Euro-score, C-reactive protein, renal function and aorta clamping time. Urine was collected within 24 hours after the onset of delirium. Matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) was applied to detect differences in the urinary proteome associated with delirium in these ICU patients. We included 10 hyperactive delirium and 10 meticulously matched non-delirium post-cardiac surgery patients. No relevant differences in the urinary excretion of proteins could be observed.

Conclusions

We conclude that MALDI-TOF MS of urine does not reveal a clear hyperactive delirium proteome fingerprint in ICU patients.

Clinical Trial Register number: NCT00604773

Background

Delirium is an acute psycho-organic syndrome, that frequently occurs in hospitalized patients and particularly in critically ill patients. This neuropsychiatric disorder is associated with serious health problems, such as prolonged stay on the mechanical ventilator, in the intensive care unit (ICU) and hospital, and a higher mortality rates (1). Three subtypes of delirium; hyperactive, hypoactive and a mixed subtype, can be distinguished based on patients Richmond Agitation Sedation Scores (RASS) (2). In daily practice, nurses and physicians experience the most difficulties with the hyperactive delirium patients who are often aggressive or even combative and in whom their delirium is associated with dislocation of their endotracheal tube and other lifesaving materials.

Although the pathophysiology of delirium is far from clear, several biomarkers and pathways, such as neuro-anatomic abnormalities, cholinergic failure, inflammatory responses and activation of the hypothalamic-pituitary adrenal axis, were found to be associated with the development of delirium (3;4). Nevertheless, suitable biomarkers that may facilitate the diagnosis of delirium have not been discovered.

Proteomics is a profiling method to detect a wide range of markers simultaneously. This technique allows the identification of several proteins potentially involved in the pathophysiological mechanism of disorders (5), such as delirium. Proteomics can be applied for determinations in tissue (6) and in several biological fluids, i.e. cerebro-spinal fluid and serum (7-9). Differences in protein profiles were detected in brain tissue of hyperactive delirium rats (significant peak at *m/z* 5030 and 5179) (10) and in the serum of delirium elderly patients with hip fracture (significant peak at *m/z* 15,900 identified as haemoglobin-β) (8). Proteomics of urine samples is of special interest, as urine reflects the low molecular weight protein pool of blood without, for mass spectrometry disturbing, abundant proteins, such as albumin (11). In addition, urine can be collected in a non-invasive way. Proteomics of urine has proven to be useful in predominantly urogenital diseases, but has recently also been implicated in non-urogenital diseases including cancer and coronary artery disease (12;13). In addition, the detection of differential protein expression in delirium patients may facilitate the understanding of the pathophysiology of disease.

The aim of our present study was to explore whether biomarkers associated with delirium could be detected in urinary protein profiles of hyperactive delirium compared to matched non-delirium ICU- patients.

Methods

Patients and delirium assessment

For this explorative study 10 hyperactive delirium post cardiac surgery patients were included and compared with 10 meticulously matched non-delirium patients. For sake of homogeneity, delirium patients after cardiac surgery were included only when they suffered from a hyperactive delirium (2), detected with the validated Dutch version of the confusion assessment method-ICU (14) by well trained ICU nurses (15). Patients were diagnosed, according to the Peterson criteria (2), as hyperactive delirium when they had only positive RASS during their delirium period. Patients were double checked by a delirium expert (MvdB) for the presence or absence of the delirium to confirm the diagnosis. To secure that only hyperactive delirium patients were included, follow-up took place until patients did not suffer from delirium anymore and only when they had positive RASS scores during their delirium period. In support of the homogeneity of the total group, patients were matched on several important risk factors for the development of delirium(16). Matching was performed on: gender, age, length of stay on the ICU at the time of urine sample collection, severity of illness score (expressed in Acute Physiology and Chronic Health Evaluation (APACHE)-II score), Creactive protein (CRP), Aorta clamping time, Euro score, serum and urine creatinine level, modification of diet in renal disease - glomerular filtration rate (MDRD-GFR) and type of operation. Patients suffering from an infection were excluded.

The local Institutional Review Board of Arnhem-Nijmegen (study number 2007/283) indicated that for this study no formal approval was required and no informed consent from patients was needed because of the observational nature of this study and the fact that no additional interventions were carried out.

This study was registered on Clinical Trial Register as NCT00604773

Sample collection, preparation and measurement

Within 24 hours after the onset of the delirium episode blood and urine were collected for creatinine measurement and urine for proteomics profiling under sterile conditions. As a control, a urine master pool was created according to Vanhoutte et al (13), which consisted of urine of 24 healthy volunteers (age 22-65 years). In brief, first-morning mid-stream urine samples were collected freshly and a master pool reference sample of all healthy volunteers was prepared by mixing together 24 urine samples containing 0.2 mmol creatinine each. Protease inhibitors were added to the urine immediately after the collection and the samples were centrifuged (15 min, 2000g at 4oC) and stored in small aliquots at -800C to minimize freeze-thaw cycles.

MALDI-TOF-MS analysis: preparation and measurement

To isolate proteins from the urine samples we used magnetic bead (MB) separation (17) with magnetic hydrophobic-interaction chromatography (MB-HIC C8), immobilized metal ion affinity chromatography (MB IMAC-Cu) and weak cation-exchange chromatography (MB WCX) beads. In addition, non-magnetic weak cation-exchange beads (CM10, Bruker Daltronics, Germany) were applied. Urine volume added to the beads was normalized to urine creatinine concentration. A urine volume of maximally 30 µL was used for MB-HIC C8 and HB IMAC-Cu; 15 µL for MB-WCX and 150 µL for CM10 beads. To all samples an internal standard of 5 µL 0.5mM hepcidin 24 was added to normalize peak intensities (18). MB purifications were performed according to the manufacturer's protocol for serum using the buffers delivered with the kit. For MB-WCX and CM10 beads other buffers were used as described by Kroot (19), based on Park (20). Pre-treated samples were transferred to a polished steel plate (Bruker Daltronics) and covered with two layers of 5 mg/mL α-cyano-4-hydroxy-cinnamic acid matrix (CHCA; Bruker Daltronics). A linear matrix-associated laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF MS Microflex, Bruker Daltronics) was used for protein profiling.

Statistics

Since the exploratory nature of this study, a power calculation for sample size calculation was not performed. Group differences were tested two-tailed using the Mann-Whitney U-test. Mass spectra data obtained after MALDI-TOF MS profiling were analyzed using ClinProt Tools Software (Bruker Daltronics), including univariate statistical analysis and unsupervised hierarchic clustering. A two tailed p value of $<.05$ was considered statistically significant.

Results

The delirium and non-delirium post-cardiac surgery ICU patients were comparable regarding the matched variables (Table 1).

Table 1 **Demographic, matched and outcome variables of delirium and non-delirium patients**

	Delirium group (N=10)	Non-delirium group (N=10)	*p-value*
Admission time (days)	1 [1-1.5]	1 [1-1]	*.91*
Gender (Male)	7	6	*.65*
Age (years)	75 [70-78]	75 [68-78]	*.73*
RASS-score (median)	0 [0 - 1]	-0.5 [-1 - 0]	*.007*
APACHE-II score	17 [14-19]	17 [13-21]	*.88*
C-reactive protein	41 [35-58]	38 [13-48]	*.28*
Aorta clamping time (minutes)	79 [63-94]	106 [66-115]	*.35*
Euro score	7 [6-9]	7 [6-12]	*.70*
Measurement Creatinine after operation in hours	21 [14-43]	21 [15-21]	*.78*
Serum Creatinine µmol/L	97 [86-114]	86 [57-125]	*.32*
Urine Creatinine µmol/L	11 [7-16]	8 [6-12]	*.25*
MDRD-GFR (ml/min/1.73m^2)	69 [55-75]	71 [52-102]	*.45*
Type of operation	CABG N=4 Valve operation N=2 Valve/CABG N=2 Miscellaneous N=2	CABG N=3 Valve operation N=1 Valve/CABG N=3 Miscellaneous N=3	*.87*

All values are median [interquartile range 25-75%] unless other reported.

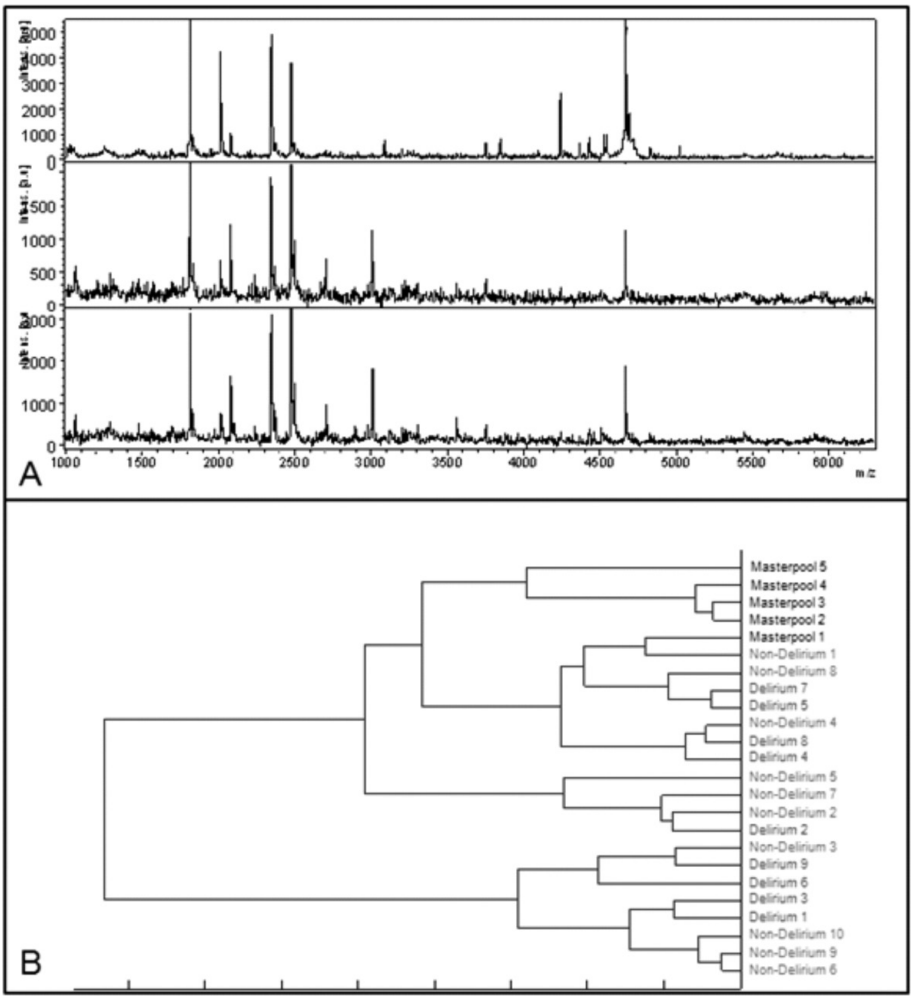
The significantly higher RASS score in the delirium group is a result of the hyperactive delirious state of these patients compared with non delirium patients. All patients were mechanically ventilated at the time of ICU admission, however, none of the patients was ventilated during the study period. Included patients did not receive any sedatives and all patients were treated with morphine according to our postoperative protocol. All blood and urine was collected in the morning, except for two patients (one in each group) in whom urine was collected in the afternoon.

Figure 1 shows representative examples of protein spectra of our master pool urine, which served as a control reference sample, a non-delirium patient and a delirium patient.

After unsupervised hierarchic clustering, the urine protein profiles of all ICU patients differed from the master pool urine protein profiles, however, a clear distinction between delirium and non-delirium patients could not be made. Urine proteomics profiling did not reveal protein patterns discriminative for delirium within the ICU patients. However, we found two protein masses to be more abundantly expressed

in the non-delirium ICU patients compared to the delirium patients as assessed by the ClinProTools.

Figure 1 **Protein spectra and hierarchical cluster after profiling with CM10 beads**



A. Protein spectra of masterpool urine (upper panel), a non-delirium patient (middle panel) and a delirium patient (lower panel). The x-axis depicts m/z values in Dalton; the y-axis shows the relative peak intensity.

B. Unsupervised hierarchical clustering determines whether patient groups can be differentiated solely based on their urine protein profile. On the right hand side the samples are represented. The lengths of the horizontal lines represent the resemblance of the spectra; the shortest lines represent the most alikeness between samples. In this hierarchic cluster our masterpool can be clearly distinguished from the ICU patients, but there is no distinction between delirium and non-delirium patients.

The clinical relevance of the 11735.7 Da ($p < .044$) mass and its suspected double charged form of 5867.12 Da ($p < .044$) in urine samples of non-delirium ICU patients is, however, questionable since these masses were found in both types of ICU patients and were highly variable. The mean mass intensity and standard deviation of 11735.7 Da in the urine of delirium ICU patients was 22.12 ± 23.47 compared to 32.1 ± 22.1 for the non-delirium ICU patients. For the 5867.12 Da mass this was 12.3 ± 12.3 versus 17.7 ± 10.7, respectively. Efforts to identify these protein masses were not undertaken because of the poor discriminative properties (viz. borderline statistical difference) in delirium ICU patients.

Discussion

This study shows no relevant differences in urine protein profiles between hyperactive delirium and matched non-delirium post cardiac surgical ICU patients. We could not reproduce the findings from previous studies that reported protein pattern specific for delirium in serum, including haemoglobin-β (8), S100-β (21;22) or other unidentified peaks at m/z 5030 and 5179 in rats withdrawn from cocaine exposure (10). This could indicate that no clear hyperactive delirium protein fingerprint is present in the urine of ICU patients or that associated proteins present in brain or serum do not pass the blood-brain-barrier or are not excreted in urine. Although mass spectrometry can be accurately applied to detect proteins over a very wide range with good sensitivity, there are some limitations to biomarker detection using proteomic protein profiling. In this study, beads were used to isolate proteins from urine and to eliminate disturbing salts for MALDI-TOF MS analysis. Disadvantages of this method are that proteins may be lost due to competition for binding to the beads and the use of beads may lead to protein selection. In addition, matrix based ionization is susceptible to signal suppression (23). Other mass spectrometry methods based on electrospray ionization, such as LC-MS/MS are less susceptible to signal suppression and have a higher sensitivity, but are also more sensitive to interfering compounds such as lipids and detergents. Moreover, LC-MS/MS is time consuming and not suitable for high-throughput screening.

To identify a biomarker pattern specific for a pathological condition it is essential to have homogeneous patients groups. Intra-group variability and the relatively small sample size may have hindered to discover differences between the patient groups. To limit this variability, kidney function and aorta clamping time (24) were meticulously matched between the studied groups. Still, ICU patients have a higher urine protein content as compared to healthy controls (mean 0.22 ± SD 0.13 g/L compared to <0.100 ± 0.002g/L in masterpool control urine samples), Challenging

the discovery of a discriminative protein in these ICU patients a challenge. In addition, the sample size of our study was relatively small, therefore there is a possibility of a type-II error. However, we did not find any clear protein profile difference between delirium and non-delirium patients, which could be an indication of a specific delirium 10 protein in the urine. Consequently we believe that the possibility of a false negative finding is very low.

Conclusion

No relevant differences in urine protein profiles between hyperactive delirium and matched non-delirium post cardiac surgical ICU was found. MALDI-TOF MS did not reveal a specific hyperactive delirium protein fingerprint in ICU patients.

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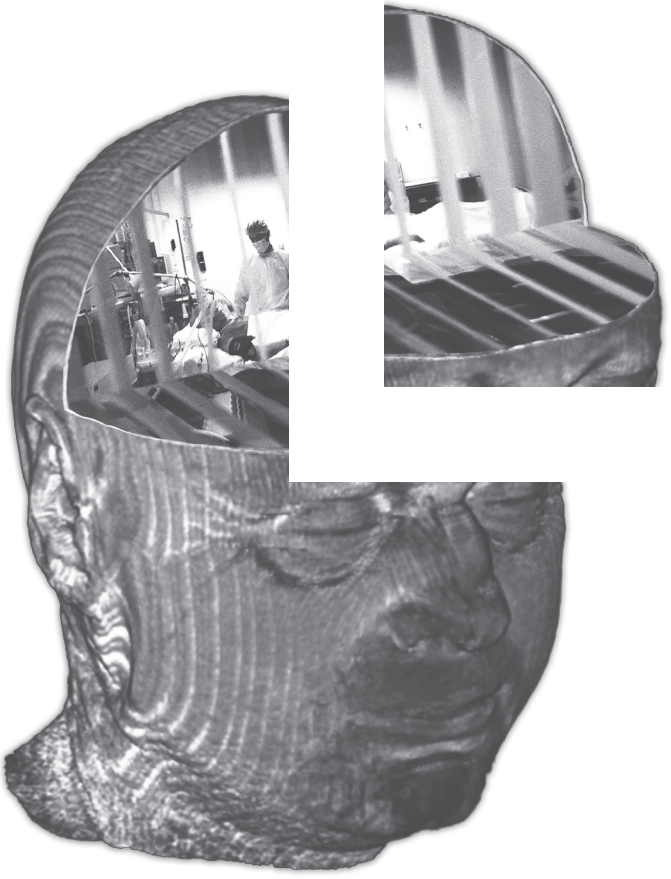

PART TWO

Impact of Delirium in Intensive Care Patients

5

Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study

Mark van den Boogaard, Lisette Schoonhoven,
Johannes G. van der Hoeven, Theo van Achterberg,
Peter Pickkers

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Abstract

Background

Delirium is a serious and frequent psycho-organic disorder in critically ill patients. Reported incidence rates vary to a large extent and there is a paucity of data concerning delirium incidence rates for the different subgroups of intensive care unit (ICU) patients and their short-term health consequences.

Objectives

To determine the overall incidence and duration of delirium, per delirium subtype and per ICU admission diagnosis. Furthermore, we determined the short-term consequences of delirium.

Design

Prospective observational study.

Participants and setting

All adult consecutive patients admitted in one year to the ICU of a university medical centre.

Methods

Delirium was assessed using the Confusion Assessment Method-ICU three times a day. Delirium was divided in three subtypes: hyperactive, hypoactive and mixed subtype. As measures for short-term consequences we registered duration of mechanical ventilation, re-intubations, incidence of unplanned removal of tubes, length of (ICU) stay and in-hospital mortality.

Results

1,613 patients were included of which 411 (26%) developed delirium. The incidence rate in the neurosurgical (10%) and cardiac surgery group (12%) was the lowest, incidence was intermediate in medical patients (40%), while patients with a neurological diagnosis had the highest incidence (64%). The mixed subtype occurred the most (53%), while the hyperactive subtype the least (10%). The median delirium duration was two days [IQR 1-7], but significantly longer ($p < .0001$) for the mixed subtype. More delirious patients were mechanically ventilated and for a longer period of time, were more likely to remove their tube and catheters, stayed in the ICU and hospital for a longer time, and had a six times higher chance of dying compared to non-delirium ICU patients, even after adjusting for their severity of illness score. Delirium was associated with an extended duration of mechanical ventilation, length of stay in the ICU and in-hospital, as well as with in-hospital mortality.

Conclusions

The delirium incidence in a mixed ICU population is high and differs importantly between ICU admission diagnoses and the subtypes of delirium. Patients with delirium had a significantly higher incidence of short-term health problems, independent from their severity of illness and this was most pronounced in the mixed subtype of delirium. Delirium is significantly associated with worse short-term outcome.

Introduction

Patients in the intensive care unit (ICU) are severely ill and need support of one or more organ functions. In the last decade, there is an increasing interest in brain dysfunctions such as delirium. Delirium is a syndrome defined as an acute onset of disturbances in consciousness and changes in cognition with a fluctuating course (1). Three subtypes of delirium can be distinguished (2). A hyperactive delirium subtype with symptoms of hyperalertness, agitation, delusions and hallucinations, a hypoactive subtype in which the patient is hypoalert, lethargic, motorically slow and has inappropriate speech and the alternating or mixed subtype. The latter subtype of delirium is characterised by alternating symptoms of hyperactive and hypoactive delirium. The Richmond Agitation Sedation Scale (RASS) ranging from +4 (heavily agitated) to -5 (coma) in combination with the delirium diagnose (3) is used to distinguish between the three delirium subtypes (2;4). Only positive RASS scores indicates a hyperactive delirium subtype. Delirious patients who only have RASS scores between 0 and -3 are defined as hypoactive delirious patients. Patients with fluctuating RASS scores, between +4 and -3 in combination with a positive delirium screening, are defined as mixed or alternating subtype. These delirium subtypes have different implications for nurses since the hyperactive subtype is easy to recognize but causes more nursing problems and inconvenience. While patients with the hypoactive subtype are, due to their lethargic state, easy to nurse but therefore also easily missed or misdiagnosed as sedation of depression (1). Meagher and Trzepactz (5;6) suggest that the different delirium subtypes in hospitalized patients represent a difference in severity of delirium. They argue that, since the duration of a hyperactive delirium is shorter than the duration of the mixed subtypes, and the length of stay in hospital is also shorter, the hyperactive subtype is less severe than the other subtypes. Whether this difference in severity of delirium is also true for ICU patients is not known.

Delirium in ICU patients is associated with short-term health consequences such as prolonged duration of mechanical ventilation and length of stay and higher mortality rates (7-9). The duration of delirium is associated with prolonged cognitive failure (10) and each additional day with delirium is associated with a 10% increase in mortality (11).

The delirium incidence in ICU patients ranges from 11 to 89% (7;9;12-14). Despite the generally high delirium incidence rate accompanied and the serious health consequences there is lack of evidence for prevention of delirium ICU patients. Preventive measures consisting of a multicomponent intervention strategy (15) and prophylactic haloperidol (16) showed positive effects in older hospitalized patients with a high risk for delirium. The effects of these preventive measures are not

determined yet in ICU patients.

The high incidence rate in critically ill patients is associated with the frequent occurrence of important risk factors for delirium (17) in ICU patients. The wide range of delirium incidence rates is likely related to case mix differences over studies. It is likely that overall delirium incidence rates and rates per subtype of delirium differ between (elective) surgical and medical patient groups. As these patient groups differ, e.g. regarding their pathophysiological disease processes, severity of illness, and chance of dying (18) we expect them to also differ in their chances of developing delirium, or chances of developing a specific subtype.

Although the classification of the delirium subtypes according to Peterson (2) is commonly used in the ICU, little is known about incidence rates of the subtypes per ICU diagnosis group and its effects on delirium duration and short-term consequences.

The aim of this study is threefold. First, to determine the delirium incidence rate overall, per subtype of delirium and per ICU diagnosis group. Second, to determine the delirium duration overall, per subtype and per ICU diagnosis group. Third, to determine differences in short-term consequences between delirious and non-delirious patients, and for the delirium subtypes and to determine the contribution of delirium to these short-term consequences.

Methods

The study was approved by the local Medical Ethical Committee (study number 2007/283), which waived the need for informed consent since no interventions were carried out. The study was registered in the Clinical trial register as NCT00604773

Study design, sample and setting

We performed a prospective cohort study between February 2008 and February 2009 in which all consecutive ICU patients were included and systematically screened for delirium. The study was carried out in the Radboud University Nijmegen Medical Centre, The Netherlands. This is a 960-bed university hospital that includes a level-3 ICU (highest level) with 33 ICU-beds for adults. Annually, approximately 2000-2500 (surgical, cardiac surgery, neurosurgical, neurological, medical, and trauma) ICU patients are admitted.

Delirium screening

Ideally, delirium is diagnosed by a psychiatrist, geriatrician or neurologist, as this is considered the 'gold standard'. However, this is not feasible in the ICU. Therefore,

several delirium assessment tools have been developed for daily use by ICU nurses. Worldwide, the validated confusion assessment method (CAM)-ICU (19;20) is mostly used and has the highest sensitivity and specificity (21). In the present study, all adult ICU patients were screened at least three times a day by trained ICU nurses (23) using the validated Dutch version of the CAM-ICU (22). Screening was performed more often if required, for example following sudden changes in behaviour, attention or consciousness. The implementation of the CAM-ICU in our daily practice is described elsewhere (23). In brief, a tailored implementation strategy was used and ICU nurses were trained at the bedside by a delirium expert nurse after they first followed one hour of group training concerning the use of the CAM-ICU. Furthermore, we used 'delirium key-nurses' for further instructions and support of the nurses. Importantly, the use of the CAM-ICU was fully supported by the medical and nursing staff. Based on the CAM-ICU result, patients were treated with haloperidol or not.

Patients were excluded for this study if: they were admitted to the ICU for less than one day; had a sustained Richmond agitation sedation score (RASS) of -4/-5 during complete ICU admission; had serious auditory or visual disorders; were unable to understand Dutch; were mentally disabled; suffered from a serious receptive aphasia or if the compliance rate of the delirium screening was <80% during a patient's stay in the ICU.

Patients who were discharged from the ICU with delirium were followed on the ward until the end of the delirium episode. On the wards, patients were screened for delirium three times a day with the delirium observation scale. This scale is developed and validated by Schuurmans (24) and is commonly used in daily practice (25).

Outcome measures

Patients were diagnosed with delirium when they had at least one positive CAM-ICU screening during their complete ICU stay. Delirium was divided in three subtypes (Figure 1). The duration of delirium was measured per 8 h shift, expressed in days and defined as time from first positive CAM-ICU until the beginning of three consecutive days of negative delirium screenings (ICU patients: negative CAM-ICU, ward patients delirium observation scale score <3). Patients who died or were discharged from the hospital while delirious were discarded for the delirium duration calculations.

The delirium incidence rate was calculated in all included ICU patients. In addition, we calculated the delirium incidence rate in patients admitted for two days or longer separately.

We defined short-term consequences of delirium as: days on the mechanical ventilator, need for re-intubation, incidence rate of unplanned removal of tubes or

catheters by the patient, length of stay (LOS) in the ICU and in-hospital, and in-hospital mortality. An extended duration of mechanical ventilation, length of stay in the ICU and in-hospital, and the in-hospital mortality were considered as the most important short-term consequences since this harms the patients directly and the most.

Patients were divided in six admission categories: cardiac surgery, neurosurgical, surgical, neurological, medical and trauma. This classification was set by the attending physician and based on main reason for ICU admission.

Variables

Demographic variables of all included patients were collected such as age, gender, admission category, severity of illness expressed in Acute Physiology and Chronic Health Evaluation (APACHE-) II score. Furthermore, delirium outcome measures and short-term consequences were collected.

Quality checks during data collection

The performance of CAM-ICU screenings by the nurses was monitored to ensure the quality of data collection. Compliance was calculated as the percentage of assessments performed per day in relation to the total number of assessments that should have been performed. The mean compliance was 90.4%. To determine the quality of the CAM-ICU performance, we measured the interrater reliability. For this, the CAM-ICU score assessed by the attending intensive care nurse was compared with the CAM-ICU score assessed by an expert psychiatry nurse within a time-window of 1 h. One hundred-and-twenty interrater reliability measurements were performed at random resulting in a Cohen's kappa of 0.90 (95%CI 0.82-0.98).

Furthermore, medical and nursing files of all patients were screened daily for signs of delirium (26). When the files contained signs of delirium without a positive CAM-ICU screening or conversely, when files did not provide evidence of delirium while there was a positive CAM-ICU score, patients were additionally screened by a delirium expert according to the DSM-IV criteria (1) to rule out false negatives and positives. These signs were for instance lethargic or depressive behaviour or just picker or agitated behaviour which was not directly recognised or screened as delirium. In total 17 patients (1.1%) were additionally screened by a delirium expert.

Finally, data-collection was randomly checked for accuracy in 15% of the patients by the first author.

Statistical analyses

Differences between delirium and non-delirium ICU patients and differences for the subtypes of delirium regarding the demographic characteristics and short-term consequences were tested non-parametrically using the Mann-Whitney U test.

Dichotomous variables were tested with the Chi-square test. To determine short-term consequences of delirium covariance analyses were performed to adjust for severity of illness. Since the distribution of the length of stay and duration of mechanical ventilation were skewed, data were log transformed resulting in normally distributed variables where after covariance analyses was performed. To take differences in duration of delirium into account, incidence rates of re-intubations, unplanned removal of catheters and the amount of removed catheters were calculated per 1000 delirium days. Differences in these incidence rates between delirium subtypes were tested using the Mann-Whitney U test.

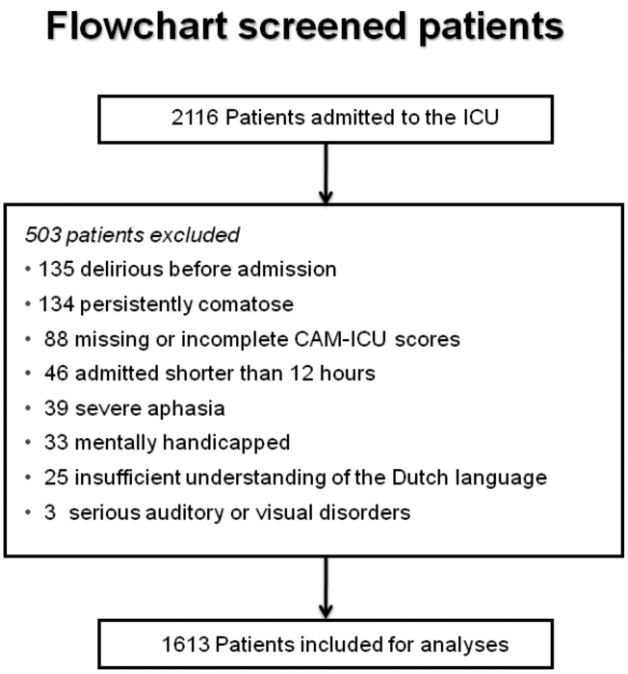
To determine the contribution of delirium to an extended duration of mechanical ventilation, length of stay in the ICU and in-hospital we used a multiple logistic regression analysis. The highest quartile of the duration of mechanical ventilation, length of stay in the ICU and in-hospital were used as cut-off value for the definition of extended duration of these variables. Important variables as delirium, age, severity of illness score, history of respiratory diseases, re-intubation and sepsis were used as covariates.

Statistical significance was defined as a p value < .05. All data were analysed using SPSS version 16.01 (SPSS, Chicago, IL).

Results

In total 2,116 consecutive patients were screened of which 503 were excluded (Figure 1). The most common reasons for exclusion were sustained coma (26.8%) and delirium before ICU admission (26.6%).

Figure 1 **Flowchart of patient inclusion**



Delirium incidence and differences between delirious and non-delirious patients

Out of the remaining 1,613 patients, 411 (26%) developed delirium during their ICU admission. When calculating the delirium incidence rate in the group of patients admitted to the ICU for two days or longer, the incidence rate increased to 53%.

Demographic characteristics of the patients are shown in Table 1. Patients with delirium were significantly older, more likely to be admitted to the ICU for urgent reasons, more likely to be mechanically ventilated and their severity of illness score was significantly higher than that of ICU patients who did not develop delirium. The delirium incidence rates of the cardiac surgery and neurosurgical groups was significantly lower compared to the other groups (all $p < .0001$), while the incidence rate in the neurology group was significantly higher than that in all other groups ($p < .05$).

Table 1 **Demographic characteristics of non-delirium and delirium patients**

	Non-delirium patients (N=1202)	Delirium patients (N=411)	*p value*
Age (years)	61 ±14	64 ±15	*< .0001*
Gender (M)	792 (66%)	235 (57%)	*.001*
Urgent admission (N)	526 (44%)	326 (79%)	*< .0001*
APACHE-II score (point)	13 ±5	18 ±6	*< .0001*
Mechanically ventilated patients (N)	903 (75%)	363 (88%)	*< .0001*
Diagnosis group			
- Cardiac surgery (N=793)	698 (88%)	95 (12%)*	
- Surgical (217)	160 (74%)	57 (26%)	
- Medical (N=360)	205 (60%)	155 (40%)	
- Trauma (N=80)	42 (53%)	38 (47%)	
- Neurology (N=89)	30 (34%)	59 (66%)**	
- Neurosurgical (N=74)	67 (90%)	7 (10%)*	

APACHE-II score: Acute Physiology and Chronic Health Evaluation-II score
Data are expressed as mean±standard deviation or numbers of patients and percentages.
** Significantly lower incidence rate than the other admission types*
*** Significantly highest delirium incidence rate*

Delirium subtypes

Regarding the delirium subtypes, the mixed subtype occurred most frequently, followed by the hypoactive delirium subtype (Table 2). The incidence of hyperactive delirium was significantly highest in the cardiac surgery group and the incidence of hypoactive delirium was significantly highest in the neurology and neurosurgical group, other differences between the delirium subtypes and admission categories are shown in Table 2.

Duration of delirium, short-term consequences and mortality

Overall the median delirium duration was 2 days [IQR 1-7, range 1-74 days] and was longest in the mixed subtype ($p < .001$). In 93 (23%) of the delirious patients it was not possible to determine the delirium duration mostly for reasons of discharge to another hospital or because the patient died. Delirious patients more likely needed respiratory support for a longer time and their ICU length of stay was longer compared to non-delirious patients (Table 3). These differences were all significant, even after adjusting for severity of illness at the time of ICU admission using the APACHE-II score. Delirious patients were significantly more likely to remove their tubes and catheters than non-delirious patients. Removal of their gastro-intestinal feeding tube occurred most frequently (51%) in patients who suffered from delirium,

followed by unplanned removal of the endotracheal tube (28%). The incidence rate of unplanned removal of tubes and catheters was significantly highest in the hyperactive subgroup delirium. This subgroup also more frequently removed tubes and catheters than the hypoactive and mixed subtype of delirium when adjusted for delirium duration.

Patients with a mixed subtype suffered the most from the short-term consequences (Table 4). Patients with the hyperactive subtype suffered the least from the short-term consequences and the delirium duration in this subtype was the shortest ($p < .0001$).

Delirious patients were six times more likely to die as compared to non-delirious patients. This difference persisted following adjustment for severity of illness. Significantly more patients with a hypoactive and mixed subtype died compared to the hyperactive subtype.

The median duration of mechanical ventilation in the total group was 0.5 days [IQR 0.3-1.0].

Table 2 **Subtypes of delirium in the six different admission categories**

	Hyperactive subtype		Hypoactive subtype		Mixed subtype	
Incidence rate	44	(11%)	148	(36%)	219	(53%)
Cardiac surgery (N=95)	22	(23%)**	38	(40%)	35	(37%)**
Surgical (N=57)	4	(7%)	16	(28%)	37	(65%)
Medical (N=155)	12	(8%)	52	(34%)	91	(59%)
Trauma (N=38)	4	(11%)	9	(24%)	25	(66%)
Neurology (N=59)	2	(3%)*	29	(49%)*	28	(48%)
Neurosurgical (N=7)	0	(0%)[#]	4	(57%)*	3	(43%)

[#] *not applicable*

* $p < .05$ ** $p < .0001$

Table 3 **Differences between non-delirium and delirium patients on short-term consequences**

	Non-delirium patients (N=1202)		Delirium patients (N=411)		*p value**
Days of mechanical ventilation	0.3	[0.2-0.6]	4.6	[0.9-10.9]	*< .0001*
Re-intubation (N)	6	(0.5)	41	(10%)	*< .0001*
Accidental removal of tubes, catheters (N)	7	(0.6)	49	(11.9%)	*< .0001*
Total number of removals (N, frequency/patient)	8	(1.1)	95	(1.9)	*.35*
LOS-ICU (days)	1	[1-2]	6	[2-13]	*< .0001*
LOS-Hospital (days)	7	[5-14]	20	[10-20]	*< .0001*
Mortality rate (N)	40	(3%)	73	(18%)	*< .0001*

LOS: length of stay

Data are expressed as medians [IQRs] or numbers of patients and percentages

** Adjusted for APACHE-II score using analysis of covariance*

The median length of stay in the ICU and in-hospital was 1 day [IQR 1-3] and 9 days [IQR 5-19], respectively. The cut-off value of extended duration of mechanical ventilation was defined as a duration longer than 1 day and an extended length of stay in the ICU, and in-hospital was defined as a stay longer than 3 days and 19 days, respectively.

Adjusting for covariates delirium was after consistently and significantly associated to an extended duration of mechanical ventilation (odds ratio 7.0), length of stay in the ICU (odds ratio 8.6) and in-hospital (odds ratio 2.1), as well as with in-hospital mortality (odds ratio 2.1)

Table 4 **Differences between subtypes of delirium in delirium incidence and duration and on short-term consequences**

	Hyperactive subtype (N=44)	*P-value* *	Hypoactive subtype (N=148)	*P-value* #	Mixed subtype (N=219)	*p value*†
Age (years, median,[IQR])	73 [60-77]	*.20**	67 [57-75]	*.75*#	66 [56-75]	*.13*†
APACHE-II score (point)	16 [13-19]	*.10**	18 [14-22]	*.47*#	18 [14-23]	*.03*†
Delirium incidence rate	44 (10.7%)		148 (36%)		219 (53.3%)	
Delirium duration (days, median, [IQR])	1 [1-1]	*< .001**	1 [1-4]	*< .001*#	4 [2-13]	*< .001*†
Mechanical ventilation (days, median, [IQR]	0.6 [0.3-2.1]	*< .001**	3 [0.8-7.7]	*< .001*#	6.9 [1.7-13.8]	*< .001*†
Re-intubation per 1000 delirium days	68	*.02**	22	*.81*#	16	*.01*†
Incidence unplanned removal tubes, catheters per 1000 delirium days	227	*< .001**	35	*.78*#	40	*< .001*†
Frequency removal of tubes per 1000 delirium days	386	*< .001**	88	*.97*#	86	*< .001*†
LOS-ICU	3 [1-5]	*.02**	5 [2-9]	*.001*#	9 [3-17]	*< .001*†
LOS in-hospital	10 [5-15]	*.003**	17.5 [8-32]	*.003*#	24 [13-48]	*< .001*†
Deceased (N)	3 (6.8%)	*.04**	28 (18.9%)	*.53*#	42 (19.2%)	*.03*†

APACHE-II score, Acute Physiology and Chronic Health Evaluation-II score. LOS, length of stay

** Difference between hyperactive and hypo active delirium subtype*

 # Difference between hypo active and mixed delirium subtype

† Difference between hyperactive and mixed delirium subtype

Table 5 **The associationa of delirium with extendedb mechanical ventilation, LOS-ICU and in-hospital, and in-hospital mortality**

	Extended mechanical ventilation OR (95%CI)	Extended LOS-ICU OR (95%CI)	Extended LOS in-Hospital OR (95%CI)	In-Hospital mortality OR (95%CI)
Delirium	7.0 (4.7-10.5)	8.6 (5.8-12.7)	2.1 (1.5-3.0)	2.1 (1.2-3.5)
Age	0.99 (0.97-1.01)	0.99 (0.98-1.01)	0.99 (0.99-1.01)	1.03 (1.01-1.05)
APACHE-II score	1.07 (1.03-1.11)	1.06 (1.03-1.1)	1.08 (1.06-1.11)	1.07 (1.03-1.11)
Sepsis	2.6 (1.2-5.6)	2.6 (1.3-5.3)	1.3 (0.8-2.2)	2.9 (1.6-5.1)
Use of sedatives	2.9 (1.8-4.6)	1.3 (0.8-2.1)	1.0 (0.7-1.5)	0.5 (0.3-0.99)
Non-sustained coma	5.6 (3.5-9.0)	3.4 (2.1-5.7)	1.3 (0.9-2.0)	1.6 (0.8-3.2)
Respiratory diseases	1.9 (1.3-2.9)	2.3 (1.6-3.4)	1.8 (1.4-2.5)	2.4 (1.5-3.9)
Re-intubation	30.1 (7.6-119.4)	18.6 (5.4-63.5)	5.6 (2.5-12.7)	1.6 0.7-3.6)

LOS, length of stay; OR, odds ratio with 95% confidence interval; APACHE-II score, Acute Physiology and Chronic Health Evaluation-II score

[a] using multiple logistic regression analysis

[b] using the highest quartile of duration was used as cut-off value

Discussion

In this study we observed that the overall delirium incidence is approximately a quarter of all ICU patients admitted for at least one day, and half of all ICU patients admitted for two days or longer. Important differences in incidence and subgroup distribution between patient categories exist. The incidence rate was the highest in the neurology group and the lowest in the cardiac- and neurosurgical group. The mixed delirium subtype occurred most frequently and also had the longest duration. The hyperactive subtype occurred the least and the duration was the shortest. Furthermore we found that delirium is associated with serious short-term health consequences, most prominently in patients with the mixed subtype. Additionally, delirium in ICU patients is significantly associated with an extended duration of mechanical ventilation, length of stay in the ICU and in-hospital, as well as with in-hospital mortality.

Our findings are of importance for clinical practice since this knowledge can contribute to taking preventive measures in patient categories with a high delirium incidence or to recognize patients who suffer the most from the consequences of delirium. To our knowledge the delirium incidence in patients admitted for neurological or neurosurgical reasons to the ICU has never been determined since these patients are mostly excluded in studies.

The high delirium incidence in ICU patients in this large prospective cohort study is in accordance with various studies (7;9;27;28), but was lower than some authors reported (8;13;29;30). Differences between these delirium incidences rates are likely related to differences in admission categories and in- or exclusion of patients with a short ICU length of stay. Indeed, we show that exclusion of patients with an ICU LOS of <2 days and ≥2 days importantly influences the incidence rate of delirium and that incidence varies greatly between diagnostic groups. Categorising the delirium incidence rate between ICU admission diagnosis group shows that there are notable differences that can be useful for others when interpreting measured delirium incidence rates.

Our results concerning the short-term consequences of delirium confirm previous work showing that delirious patients are mechanically ventilated for a significantly longer time (31), have a longer ICU and in-hospital length of stay (8) and are more likely to die (28;32). However, none of these studies reported differences between the subtypes of delirium. Overall, delirious patients had significantly more short-term health problems than non-delirious patients and these problems were most profound in the mixed subtype, which also had the longest duration.

Regarding these subtypes of delirium, the hyperactive subtype occurred the most in cardiac surgery patients, this subtype had the shortest duration and the fewest

short-term consequences compared with the hypoactive and mixed subtype. However in practice, nurses and physicians experience the most difficulties with patients with this easily recognizable delirium subtype. These patients are often agitated and consequently pull out their lines or endotracheal tube. Adjusted incidence rates of re-intubation and unplanned removal of catheters and tubes confirm these experiences of caregivers.

We found several significant differences for delirium subtypes and admission categories of which difference between the incidence of hyperactive delirium in the cardiac surgery and neurosurgical group is remarkable. There are only a few studies which reported incidence rates of delirium subtypes but these were only in medical (2) or surgical and trauma patients (4). Except for the higher incidence rate in the hyperactive group in our study, mainly caused by the high incidence rate in cardiac surgery patients, the numbers of the hypoactive and mixed subtype of delirium are rather comparable with these other reports.

Some limitations of this study need to be considered. Firstly, we did not use the 'gold standard' to diagnose delirium, but the CAM-ICU, which is a delirium screening tool. This screening tool is however, the most frequently used tool worldwide, and has the highest sensitivity and specificity and a high inter-rater reliability (21;33). Moreover, to secure that no false negative or positive delirium assessments were used for the calculations in this study we also checked patients' files and if necessary a delirium expert additionally screened these patients. Therefore, we believe our assessment is valid and our incidence rate is reliable. However, one may argue that our overall incidence rate is low compared to other studies on delirium in the ICU, and hence may not be reliable. We attribute this low incidence to the fact that we included a large number of cardiac surgical patients, of which most have an ICU stay of one day and a low incidence of delirium (34;35). When we excluded the patients with an ICU stay of only one day our incidence rate became comparable to that of other studies. Secondly, we excluded more than 20% of our screened patients. For this study we used similar exclusion criteria as others did when using the CAM-ICU (8;36). The most frequent reason for exclusion was 'delirious before ICU admission' which must be considered as a normal exclusion criteria when determining the incidence rate. Sustained coma was the second most frequent reason which occurred the most in neurological patients. This patient category is mostly excluded in other studies. Despite we included also patients admitted to the ICU for a neurological disease, we excluded a similar amount of patients when compared with other studies which ranges up to 43% (7;9;32;37).

Thirdly, in this prospective cohort study we determined that delirium is associated with several short-term consequences which does not necessarily indicate there is a causal relationship between delirium and the outcome parameter. Our study

design is too limited to draw these strong conclusions. Despite this limitation it is important to recognize that delirium is a serious disorder with serious short-term consequences and our results corroborates findings of other smaller studies (8;11;32).

Lastly, in our study a notable number of patients died or were discharged to other hospitals before the end of the delirium episode and like others (38) we did not include the residual duration of their delirium period. One may argue that this resulted in an underestimation of the delirium duration and unplanned removal of tubes and catheters. Although this could have influenced the delirium duration, this calculation method will not influence the incidence of unplanned removal of tubes and catheters as all these patients were already discharged from the ICU to the ward and therefore had less indwelling tubes and catheters.

Conclusion

Over a quarter of our ICU population with a length of stay >1 day and half of the ICU patients with a length of stay of ≥2 days developed delirium during their ICU stay. There is an important difference between admission categories concerning the delirium incidence rates and the occurrence of subtypes of delirium. Patients who developed delirium were significantly more likely to suffer from short-term health problems and had a six times higher chance of dying compared to ICU patients who did not develop delirium, independently of their severity of illness. The problems were most pronounced in patients with a mixed subtype of delirium.

In summary, the high delirium incidence rate and serious short term health related problems for patients must be sufficient to convince health care professionals to screen patients for delirium and should encourage nurses to take preventive measures such as cognitive stimulation (15), music therapy (39), prophylactic haloperidol (16;40) or early mobilization (41) of which the latter is the only measure which was examined in ICU patients.

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6

The impact of delirium on the prediction of in-hospital mortality in intensive care patients

Mark van den Boogaard, Sanne A.E. Peters,
Johannes G. van der Hoeven, Pieter C. Dagnelie, Pieter Leffers,
Peter Pickkers, Lisette Schoonhoven

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ABSTRACT

Introduction

Predictive models, such as acute physiology and chronic health evaluation II (APACHE-II), are widely used in intensive care units (ICUs) to estimate mortality. Although the presence of delirium is associated with a higher mortality in ICU patients, delirium is not part of the APACHE-II model. The aim of the current study was to evaluate whether delirium, present within 24 hours after ICU admission, improves the predictive value of the APACHE-II score.

Methods

In a prospective cohort study 2116 adult patients admitted between February 2008 and February 2009 were screened for delirium with the confusion assessment method-ICU (CAM-ICU). Exclusion criteria were sustained coma and unable to understand Dutch. Logistic regression analysis was used to estimate the predicted probabilities in the model with and without delirium. Calibration plots and the Hosmer-Lemeshow test (HL-test) were used to assess calibration. The discriminatory power of the models was analyzed by the area under the receiver operating characteristics curve (AUC) and AUCs were compared using the Z-test.

Results

1740 patients met the inclusion criteria, of which 332 (19%) were delirious at the time of ICU admission or within 24 hours after admission. Delirium was associated with in-hospital mortality in unadjusted models, odds ratio (OR): 3.22 (95% confidence interval [CI]: 2.23 - 4.66). The OR between the APACHE-II and in-hospital mortality was 1.15 (95% CI 1.12 - 1.19) per point. The predictive accuracy of the APACHE-II did not improve after adding delirium, both in the total group as well as in the subgroup without cardiac surgery patients. The AUC of the APACHE model without delirium was 0.77 (0.73 - 0.81) and 0.78 (0.74 - 0.82) when delirium was added to the model. The z-value was 0.92 indicating no improvement in discriminative power, and the HL-test and calibration plots indicated no improvement in calibration.

Conclusions

Although delirium is a significant predictor of mortality in ICU patients, adding delirium as an additional variable to the APACHE-II model does not result in an improvement in its predictive estimates.

INTRODUCTION

Predictive models are widely used in ICUs to estimate the disease severity and estimate the risk of death or to identify patients at high risk of dying (1). Predictive estimates are important from both a clinical and administrative perspective. These estimates can be used to inform patients and their families about likely outcomes (1;2), to monitor response to treatment, to guide physicians in making clinical decisions (2), and to monitor or compare the performance of different ICUs (3). A commonly used prediction model in the ICU is the Acute Physiology and Chronic Health Evaluation (APACHE)-II (4), which is measured within 24 hours of ICU admission. Importantly, although the APACHE-II score was developed in the early 1980s, it still represents the most widely used predictive model to estimate in-hospital mortality and it remains a valid measure of severity of illness. The APACHE-II is able to correctly differentiate between patients who are and who are not at risk of dying in 62% to 88% of patients (5). The Glasgow Coma Scale is the only variable referring to brain (dys)function in the APACHE-II score (4). Delirium, another brain disorder, is not included in the APACHE-II model, despite its high incidence rate in ICU patients and the growing evidence of its association with poor outcomes such as increased morbidity and mortality rates, and prolonged length of hospital stay (6;7).

Delirium, defined as a disturbance of consciousness and cognition that develops over a short period of time and fluctuates over time, is induced by an underlying physical cause such as the development of severe medical illness, co-morbidities and changes in drug use (8;9). One-third of patients are delirious on initial assessment, and the majority who develop delirium do so within 48 hours of admission (8).

Consequently, adding delirium to the existing APACHE-II model could improve the predictive estimates. However, despite the strong association between delirium and mortality, such an association does not necessarily imply clinical relevance or better prediction.

The aim of our study was to evaluate whether delirium, if present within 24 hours after ICU admission, improves the predictive accuracy of the APACHE-II score of in-hospital mortality of critically ill patients.

Material and methods

This prospective cohort study was carried out in the Radboud University Nijmegen Medical Centre, the Netherlands. This is a 960 bed university hospital with 33 ICU beds for adults where annually 2,000 to 2,500 (cardiothoracic surgery, neurosurgical, medical, surgical and trauma) ICU patients are admitted. The study was approved by the local Medical Ethical Committee, which waived the need for informed consent because no interventions were carried out.

Consecutive adult patients admitted to the ICU between February 2008 and February 2009 were included. Patients were excluded when they had a sustained Richmond agitation sedation score (RASS) of -4/-5, length of stay on the ICU for 12 hours or less, had serious auditory or visual disorders, were unable to understand Dutch, were severely mentally disabled or suffered from receptive aphasia.

To detect delirium, all patients were screened with the validated Dutch version of the Confusion Assessment Method-ICU (CAM-ICU) (10). The assessment with the CAM-ICU was performed three times per day by well trained ICU nurses during the patient's entire ICU stay (11). For this study patients were diagnosed with delirium when they had a minimum of one positive CAM-ICU screening assessment. As for the other parameters used in the APACHE-II score, we used delirium that occurred within 24 hours after ICU admission. Demographic, laboratory, clinical data, and hospital mortality were collected. Naturally, various risk factors for the development of delirium may differ between patients, but these were not registered because the aim of the present study was merely to investigate if the predictive value of the APACHE-II score improved when delirium, irrespective of its cause, was added.

As the APACHE-II was originally not validated for cardiac surgery patients, a subgroup analysis was also performed without cardiac surgery patients.

Statistical analysis

Patient characteristics at baseline and the incidence of delirium within 24 hours, and in-hospital mortality were evaluated. Normally distributed data were tested parametrically using the Student's T-test, and not normally distributed data were tested non-parametrically using the Mann-Whitney U test. The correlation between delirium and the APACHE-II score was tested using the Spearman's rho. The association between delirium and in-hospital mortality was evaluated in a univariate and multivariate logistic regression model. The first model consisted of patient's overall score on all variables of the APACHE-II score as the only predictive variable. The second model, based on the data of the same patients, consisted the variables of the APACHE-II score with delirium added as a new predictor. Differences in model performance between the APACHE-II model with and without

delirium were estimated on discrimination (area under the receiver-operating-characteristic (AUC) curve). The two AUCs were compared using the z-statistic for comparing AUCs derived from the same cases as described by Hanley and McNeil (12). A z-value between -1.96 and +1.96 was considered as there being no significant differences between the two AUCs and with the most common used features on calibration (Hosmer-Lemeshow's goodness-of-fit and calibration plots). A two-sided significance level of 5% and 95% confidence intervals (CI) were used for statistical inference. Statistical analysis was performed using SPSS 16.01 and MedCalc® version 11.3.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

During the study period, 2,116 patients were admitted to the ICU of whom 376 patients were excluded, leaving 1,740 patients for outcome analysis. The main reason for exclusion was persistent coma (36%) that made the detection of delirium impossible. Baseline characteristics of the included patients, with and without delirium within 24 hours, are shown in Table 1, and baseline characteristics of the patients, with and without cardiac surgery patients, are shown in Table 2.

Table 1 **Baseline characteristics and differences of delirious (within 24 hours after ICU admission) and non-delirious patients***

	Non-delirium <24 hours	Delirium <24 hours	*p value*
Age in years	61 ± 15	66 ± 14	*.11*
Male, N (%)	134 (21.1)	198 (17.9)	*.08*
APACHE-II score	14 ± 6	17 ± 6	*.18*
Length of stay-ICU in days (median-IQR)	1 (1-3)	3 (1-9)	*< .0001*
Length of stay-hospital in days (median-IQR)	8 (5-16)	15 (8-33)	*< .0001*
Urgent admission, N (%)	708 (50.3)	253 (76.2)	*< .0001*
ICU admission type (%):			
- Surgical	910 (87.7)	127 (12.2)	
- Medical	302 (70.1)	129 (29.9)	
- Trauma	66 (78.6)	18 (21.4)	
- Neurology/neurosurgical	130 (69.1)	58 (30.9)	
Died, N (%)	80 (5.7)	54 (16.2)	*< .0001*

APACHE, Acute Physiology and Chronic Health Evaluation-II; IQR, interquartile range.
** Data are presented as mean ± standard deviation, unless otherwise mentioned.*

A total of 332 patients (19%) were delirious, 132 at the time of admission and 200 within 24 hours after admission. The overall in-hospital mortality rate was 7.7%. In the non-delirious group 80 of 1,408 patients (5.7%) died, and in the delirious group this was 54 of 332 patients (16.2%).

Table 2 **Baseline characteristics of the patients in the total group and the subgroup without cardiac surgery patients ***

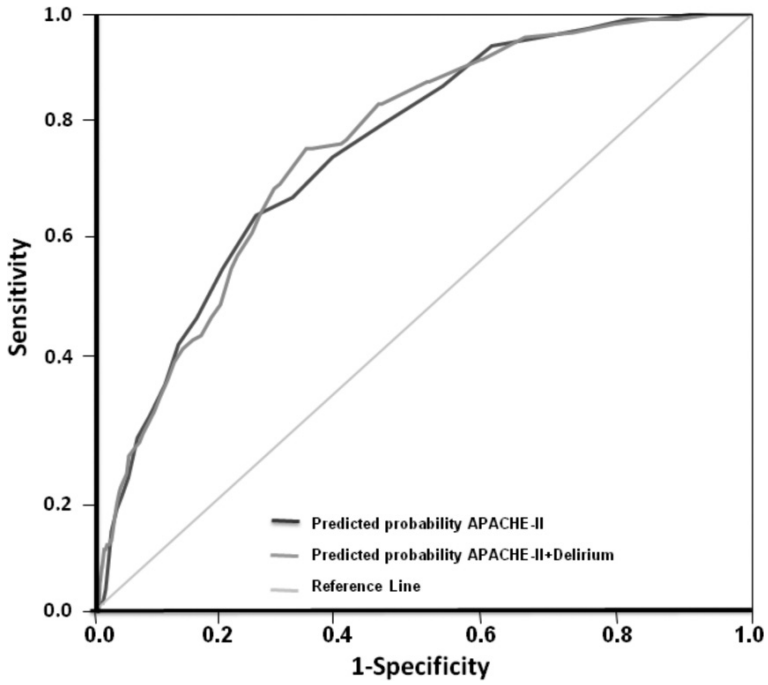
	Total group N = 1740	Non-cardiac surgery patients N = 881
Age in years	62 ± 14	58 ± 16
Gender M/F, N	1109/631	506/375
APACHE-II score	15±5	16±6.6
Length of stay-ICU in days (median-IQR)		
- non delirious (within 24 hours after admission)	1 (1-3)	2 (1-7)
- delirious	3 (1-9)	3 (2-10)
Length of stay-hospital in days (median-IQR)		
- non delirious (within 24 hours after admission)	8 (5-16)	14 (8-27)
- delirious	15 (8-33)	19 (10-36)
Urgent admission, N (%)	961 (55.2)	703 (82.8)
ICU admission type (%):		
- Surgical	59.6	23.4
- Medical	24.8	45.9
- Trauma	4.8	9.4
- Neurology/neurosurgical	10.8	21.3
Delirium, N (%)	332/1740 (19.1)	223/881 (25.3)
- before admission	132 (7.6)	106 (12.0)
- within 24 hours after admission	200 (11.5)	117 (13.2)
Died, N (%)		
- non delirious (within 24 hours after admission)	80 (5.7)	71 (10.8)
- delirious	54 (16.2)	36 (16.1)

APACHE, Acute Physiology and Chronic Health Evaluation-II; F, female; IQR, interquartile range; M, male.

** Data are presented as mean ± standard deviation, unless otherwise mentioned.*

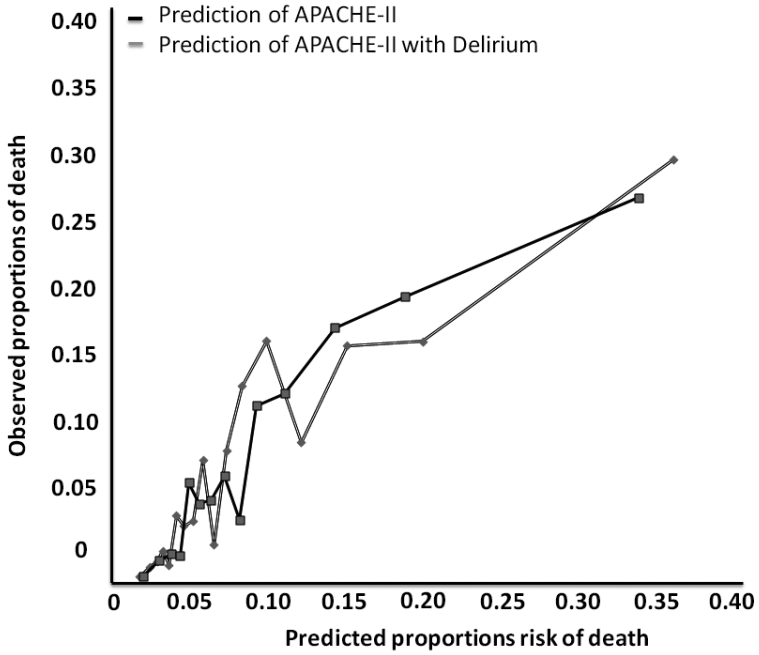
The crude odds ratio (OR) of the presence of delirium within 24 hours of ICU admission and in-hospital mortality was 3.22 (95% CI: 2.23 to 4.66), and between the APACHE-II score and in-hospital mortality was 1.15 (95% CI: 1.12 to 1.19) per APACHE-point. The AUC of the APACHE-II model without delirium was 0.77 (95% CI: 0.73 to 0.81, standard error 0.19) and 0.78 (95% CI: 0.74 to 0.82, standard error 0.19) when delirium was added. Comparison of the two AUCs with the Hanley and McNeil test resulted in a z-value of 0.92 (p = .36) indicating that both AUCs were not significant different and that addition of delirium to the APACHE-II score does not result in an improvement in discriminative power (Figure 1).

Figure 1 **Receiver-operating-characteristic and the area under the curve of different prediction models with and without delirium. APACHE-II, Acute Physiology and Chronic Health Evaluation-II.**



Calibration plots (Figure 2) and the Hosmer-Lemeshow test (HL-test) showed a decrease of calibration after adding delirium to the APACHE-II score (HL-test chi-square 12.38 and after adding delirium to the APACHE-II chi-square 17.93). The Spearman's rho correlation between delirium and the APACHE-II score was 0.22 (p < .0001). The subgroup, in which cardiac surgery patients were excluded, consisted of 881 patients. The crude OR for delirium present within 24 hours after ICU admission and in-hospital mortality in this subgroup was 1.59 (95% CI: 1.03 to 2.46) and for APACHE-II and in-hospital mortality was 1.11 (95% CI: 1.08 to 1.15) per point.

Figure 2 **Calibration plots of the APACHE-II model and of the APACHE-II model with delirium. APACHE-II, Acute Physiology and Chronic Health Evaluation-II**



Discussion

The main finding of the present study is that, although delirium present within 24 hours after ICU admission, is associated with increased in-hospital mortality, adding delirium to the APACHE-II score does not improve its accuracy in predicting in-hospital mortality. Similar results were obtained in a subgroup analysis of non-cardiac surgery patients.

The availability of an easy to use instrument that needs a limited amount of variables to predict the outcome of ICU patients is of great importance for clinical ICU practice. The APACHE-II score represents such an instrument with a moderate predictive value for in-hospital mortality. Comparable with previous reports (5) we found an AUC of the APACHE-II of 0.77. Theoretically, adding a prevalent and relevant variable to the APACHE-II score could improve its predictive value. Delirium could represent such a variable, because it is a frequent and serious disorder on the ICU associated with poor patient outcome. Although our study confirms previous reports (13), showing that the presence of delirium is an independent risk factor

for mortality, we demonstrate that the addition of delirium does not improve the predictive value of the APACHE-II score. There are several reasons why adding a new predictive variable may not result in a better accuracy of a predictive model including a low prevalence of the variable, the absence of predictive value of this variable, and the presence of a correlation between the predictive variable and the variable(s) originally included in the predictive model (i.e. APACHE-II). We showed that prevalence and predictive value of the presence of delirium are adequate. However, although the occurrence of delirium in critically ill patients is an independent risk factor for mortality (14), we found that the APACHE-II score correlated significantly with the occurrence of delirium within 24 hours. As a consequence, delirium has no additive effect in the predictive value of the APACHE-II score.

Importantly, our data do not exclude a possible additive effect of incorporating delirium in models that are not focused on the first 24 hours of ICU stay, such as the sequential organ failure assessment (SOFA) score. Although there is a statistically significant association between delirium present within 24 hours after ICU admission and APACHE-II score, an association of 0.22 is rather low. Probably residual confounding plays an important role. The effect of adding delirium to dynamic predictive models such as the SOFA score, warrants further investigations because in a substantial part of the patients delirium is detected after the first 24 hours after ICU admission as a result of worsening of their clinical situation.

Conclusion

An independent association was found between delirium present within 24 hours after ICU admission and in-hospital mortality. However, adding delirium as a predictive variable to the APACHE-II score did not improve its predictive value.

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7

Delirium in critically ill patients: impact on long-term health related quality of life and cognitive functioning

Mark van den Boogaard, Lisette Schoonhoven,
Andrea W. Evers, Johannes G. van der Hoeven,
Theo van Achterberg, Peter Pickkers

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Abstract

Objective

To examine the impact of delirium during their ICU stay on long-term health-related quality of life and cognitive function in intensive care survivors.

Design

Prospective 18-month follow-up study.

Setting

Four intensive care units of a university hospital.

Patients

A median of 18 months after intensive care discharge, questionnaires were sent to 1292 intensive care survivors with (n=272) and without (n=1020) delirium during their intensive care stay.

Measurements and Main Results

The short form-36v1, checklist individual strength-fatigue and cognitive failure questionnaire were used. Covariance analysis was performed to adjust for relevant covariates. Of the 915 responders, 171 patients were delirious during their intensive care stay (median age 65 [interquartile range 58-85], Acute Physiology and Chronic Health Evaluation-II score 17 [interquartile 14-20]), and 745 patients were not (median age 65 [interquartile 57-72], Acute Physiology and Chronic Health Evaluation-II score 13 [interquartile 10-16]). After adjusting for covariates, no differences were found between delirium and nondelirium survivors on the short form-36 and checklist individual strength-fatigue. However, survivors who had suffered from delirium reported that they made significantly more social blunders and their total cognitive failure questionnaire score was significantly higher compared to survivors who had not been delirious. Survivors of a hypoactive delirium subtype performed significantly better on the domain mental health than mixed and hyperactive delirium patients. Duration of delirium was significantly correlated to problems with memory and names.

Conclusions

Intensive care unit survivors with delirium during their intensive care unit stay had a similar adjusted health-related quality of life evaluation, but significantly more cognitive problems than those who did not suffer from delirium, even after adjusting for relevant covariates. In addition, the duration of delirium is related to long-term cognitive problems.

Introduction

Delirium is a disorder that frequently occurs in intensive care unit (ICU) patients (1-3) and is recognized as acute brain dysfunction with changes in consciousness and cognition which fluctuate during the day (4). This disorder is associated with serious health problems and long-term cognitive impairment (5;6). Generally, without distinguishing between delirium and nondelirium patients, 25 to 78% of ICU patients experience cognitive impairments after discharge from the ICU (7) emphasizing the need for more attention in the period following critical illness. There is a growing interest in Health Related Quality of Life (HRQoL) after ICU discharge (8-13). HRQoL questionnaires are usually subdivided into dimensions relating to physical, mental and social functioning. It is recognized that the value of measurements of cognitive functioning with a general HRQoL questionnaire is limited in this setting and specific surveys measuring patients cognitive functioning, such as the validated self-reporting cognitive failure questionnaire (CFQ) (14), have been developed.

Only two studies have examined the impact of delirium on HRQoL in ICU survivors (6;13). These studies were rather small, relatively short with a maximum follow-up of 3 and 12 months, and no analyses of the delirium subtypes were performed (6;13). A significant difference between delirium and nondelirium patients in role-physical function, which mostly reflects functioning in daily activities, was reported (13), however no correction for disease severity was performed (13). This implies that these findings could be the result of an epiphenomenon. The duration of delirium during patients' ICU stay was associated with their observed impaired cognitive performance (6). Little is known about the long-term (>1 yr) effects of delirium on aspects of the HRQoL in this specific group of patients. In addition, it is unknown if there are differences in HRQoL (including cognitive function) for subtypes of delirium (3) and if there is a correlation between the duration of delirium and HRQoL.

Therefore, the aim of this study was to compare the HRQoL, including selfreported cognitive functioning, in ICU survivors with delirium during their ICU stay with those that did not suffer from delirium, after a median of 18 months after ICU discharge. Furthermore, we examined the correlations between duration of delirium and HRQoL, and if subtypes of delirium exerted different effects on HRQoL.

Material and methods

Subjects

All consecutive patients admitted to the intensive care unit of the Radboud University Nijmegen Medical Centre between February 2008 and February 2009 were screened for delirium three times a day with the confusion assessment method (CAM)-ICU (1;15) by well trained ICU nurses (16). In February 2010, after a median duration of 18 months after ICU discharge, we evaluated the health related quality of life of the surviving patients. The regional Medical Ethical Committee approved the study (study number 2010/008) and waived the need for informed consent, since the objective of this study was to evaluate regular patient care.

Procedures

All ICU patients were included in this study except those: admitted for < 1 day; were suffering from sustained coma on the ICU; had serious auditory or visual disorders; were unable to understand Dutch; were severely mentally disabled; were suffering from a serious receptive aphasia; or whose delirium screening was not complete during their ICU stay. Patients were diagnosed with delirium when they had at least one positive CAM-ICU screening during their complete ICU stay, as previously described (17;18). To secure the quality of the delirium diagnosis medical and nursing files of all patients were also screened daily for signs of delirium (19). When the files contained signs of delirium without a positive CAM-ICU screening, patients were additionally screened by a delirium expert according to the DSM-IV criteria (4) to rule out false negatives and positives. In total, 17 patients (1.1%) were additionally screened this way by a delirium expert. Patients with delirium were divided in three subtypes (3): hyperactive delirium subtype with symptoms of hyper alertness and agitation (Richmond Agitation Sedation Scale +1/+4), hypoactive subtype in which the patient is hypoalert, lethargic (Richmond Agitation Sedation Scale 0/-3), and the alternating or mixed subtype (Richmond Agitation Sedation Scale +4/-3). This last subtype of delirium is characterised by alternating symptoms of hyperactive and hypoactive delirium.

Demographic variables as well as data of severity of illness, delirium duration and delirium subtype of these patients were collected.

At median 18 months after ICU discharge, an HRQoL survey was sent out to the cohort of ICU survivors. Four weeks after this a reminder letter was sent to the nonresponders. We used three different validated instruments to measure the HRQoL. We will refer to these three tests as the HRQoL. Although there is no specific HRQoL instrument for ICU-patients, recommended instruments for ICU patients are the short form-36 (SF-36) and the EuroQoL-5D (20). We used the validated

Dutch version of the short form-36 (SF-36) version 1 (21) containing eight multi-item dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Aggregated summary scores were calculated for physical and mental functioning expressed in physical component score and mental component score, respectively. To calculate the physical component score and mental component score, we used the standardized Dutch population scores (22). In line with the SF-36 Health Survey Manual (23) missing values were imputed, data were recoded and subsequently scored (range 0 to 100). A higher score indicates a higher level of functioning. Additionally, the shortlist of the Dutch validated checklist individual strength-fatigue (CIS)-fatigue, consisting of 8 questions scoring on a 7 point Likert scale (24), was used. The range of the CIS-fatigue is 8 to 56, a higher score indicating more pronounced fatigue. The third instrument was the validated Dutch translation (25) of the cognitive failure questionnaire (CFQ) which is a self-reported cognitive functioning questionnaire. This questionnaire consists of 25 questions (14). The self-reported CFQ measures consist of four dimensions (26) of cognition: memory, distractibility, social blunders, and names. Each question of the CFQ was scored on a 5-point Likert scale. The total score on the CFQ ranges from 0 to 100, a higher score indicates more self-reported cognitive dysfunction. Thus, our self-reported HRQoL survey consisted of a total of 69 questions which took an estimated 45-60 mins to answer.

To guarantee the patient's privacy, the survey was sent out anonymously and numbered. This allowed the primary and supervising investigator to match the returned survey with the patient's registry number in a separate confidential database.

Statistical analyses

The differences between those who suffered from delirium and nondelirium ICU survivors were tested nonparametrically using the Mann-Whitney *U* test. Dichotomous variables were tested with the chi-square test. Since the results of our HRQoL were non-normally distributed, log transformation of all HRQoL data was carried out successfully and the duration of delirium was divided into quartiles, resulting in normally distributed outcome measurements. The correlation between duration of delirium divided into quartiles and the log transformed HRQoL was tested using Pearson's correlation coefficient. Significant differences in demographic variables between nondelirium and delirium patients and differences between the delirium subtypes were considered as covariates and a multivariate analysis of covariance was performed. Since there was no difference in age between delirium and nondelirium responders in our population, adjusting for age was unnecessary. In view of the explorative nature of this study, and to increase its sensitivity, no

correction for multiple testing was performed.

Statistical significance was defined as a p value < .05. All data were analyzed using SPSS version 16.01 (SPSS, Chicago, IL).

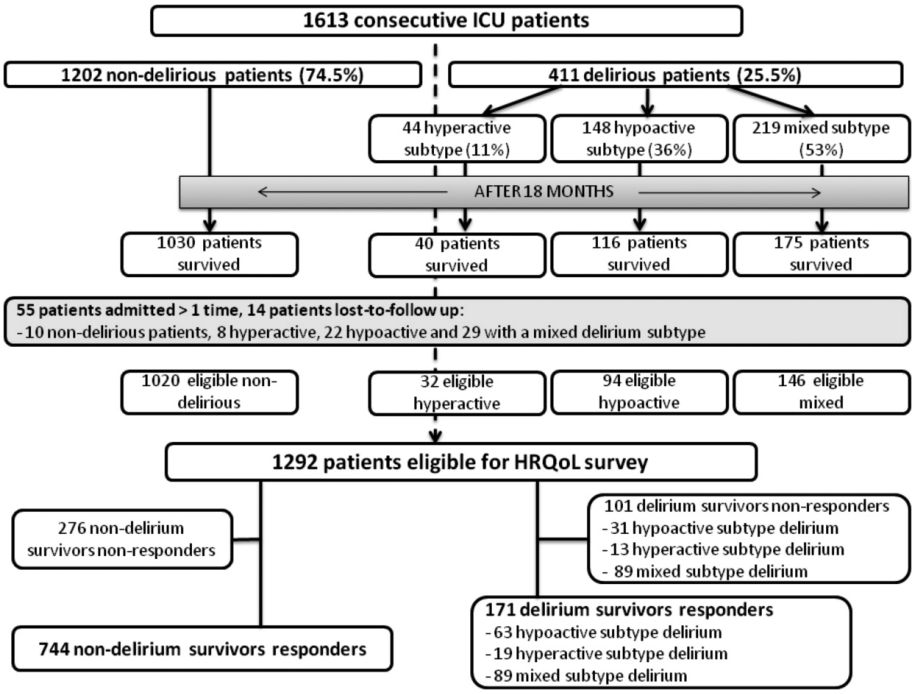
Results

At the median of 18 months prior to this HRQoL survey, a total of 1,613 consecutive patients who fulfilled the inclusion criteria were admitted (Figure 1). In this group 1,202 patients had no delirium and 411 were delirious during their ICU stay. Overall 183 patients died, of whom 58 (5%) had not been delirious and 80 (19%) had. The hypoactive delirium subgroup had a similar number of survivors as compared to the mixed subgroup, while survival was significantly higher (p = .02) in the hyperactive subgroup (Figure 1), a median 18 months after ICU discharge. In total, 55 patients were admitted to the ICU more than once and 14 patients were lost to follow-up.

In total, there were 1,292 ICU survivors (Figure 1) of whom 272 patients (21%) suffered from delirium during their ICU stay and 1,020 patients did not. In the delirious group seven patients (3%) with a hyperactive subtype of delirium had one positive CAM-ICU screening, and 264 patients had at least two positive CAM-ICUs during their ICU stay.

Median 18 months (interquartile range 15-21) after ICU discharge a total of 915 out of the 1,292 eligible patients (71%) returned the questionnaire. Of these responders 171 out of 272 (63%) patients suffered from delirium during their ICU stay and 744 out of 1,020 (73%) did not.

Figure 1 **Flowchart of included patients for the Health Related Quality of Life survey**



Seven hundred eighty-eight survivors completed all questionnaires, 91% completed the SF-36, 98% completed the CIS-fatigue and 97% answered all the questions of the CFQ. The demographic data and illness-related characteristics of the responders and nonresponders are illustrated in Table 1.

Responders with delirium during their ICU stay were significantly more likely to be admitted for urgent reasons and for sepsis, were more likely to be female than male, had a higher Acute Physiology and Chronic Health Evaluation-II score and their ICU and hospital length of stay was significantly longer compared to patients that did not develop delirium during their ICU stay (Table 2).

Differences between delirium and nondelirium patients on HRQoL: SF-36

Eighteen months (median 18, interquartile range 15-21) after ICU discharge, patients with delirium during their ICU stay rated their quality of life lower on all dimensions of the SF-36 and the physical and mental component scores compared to patients who did not have delirium (Table 3). However, when adjusted for the covariates Acute Physiology and Chronic Health Evaluation-II score, sepsis, ICU length of stay, gender and urgent admission, no statistically significant differences between groups

remained. The results of our ICU survivors were worse on several domains of the SF-36 compared with an age-adjusted general Dutch population (Table 3) and are in line with those of others (10).

Table 1 **Demographic characteristics of responders and non-responders**

	Responders (n=915)	Non-responders (n=377)	*p*
Age	65 [57-72]	60 [47-71]	*< .0001*
Delirium (n=272)	171 (19%)	101 (27%)	*.001*
- Hypo active (n=94)	63 (7%)	31 (8%)	
- Hyperactive (n=32)	19 (2%)	13 (3%)	
- Mixed (n=146)	89 (10%)	57 (15%)	
Gender (male)	609 (67%)	231 (61%)	*.005*
Sepsis (n)	28 (3%)	11 (3%)	*.53*
Urgent admission (n)	389 (43%)	204 (54%)	*< .0001*
Acute Physiology and Chronic Health Evaluation-II score	14 [11-17]	13 [10-17]	*.06*
LOS-ICU (days)	1 [1-2]	1 [1-3]	*.03*
LOS-Hospital (days)	7 [5-14]	9 [6-18]	*.001*
Admission type			*< .05*
- Surgical	666 (73%)	225 (59%)	
- Medical	131 (14%)	74 (20%)	
- Trauma	41 (5%)	32 (9%)	
- Neurology/Neurosurgical	77 (8%)	46 (12%)	

Data are expressed as median with IQR unless other reported

Table 2 **Demographic characteristics of responders**

	Nondelirium Patients (n=744)		Delirium Patients (n=171)		*p*
Age	65	[57-72]	65	[58-75]	*.13*
Gender (male)	508	(68%)	101	(60%)	*.01*
Acute Physiology and Chronic Health Evaluation-II score	13	[10-16]	17	[14-20]	*< .0001*
Urgent admission (n)	261	(35%)	128	(75%)	*< .0001*
Length of stay-intensive care unit (days)	1	[1-1]	5	[2-11]	*< .0001*
Length of stay-hospital (days)	7	[5-11]	16	[9-37]	*< .0001*
Sepsis (n)	12	(2%)	16	(9%)	*< .0001*
Admission type					*< .01*
- Surgical	589	(79%)	77	(45%)	
- Medical	77	(10%)	54	(32%)	
- Trauma	24	(3%)	17	(10%)	
- Neurology/Neurosurgical	54	(7%)	23	(14%)	

Data are expressed as median with IQR unless other reported

Differences between delirium and nondelirium patients on HRQoL: CIS-fatigue

Patients who suffered from delirium experienced more problems with physical exertions expressed in a higher total CIS score, compared to the nondelirium patients (Table 3). Again, after adjusting for covariates, no significant differences in the CIS scores between the two groups remained.

Differences between delirium and nondelirium patients on HRQoL: CFQ

The delirium survivors reported more pronounced cognitive failure on all measured cognitive dimensions compared to patients who did not suffer from delirium. Even after adjusting for covariates this difference between the groups persisted. Adjusted for covariates, patients who had previously had delirium tended to experience more problems with their memory (p = .08). Overall, their total self-reported cognitive function was significantly impaired. In addition, patients with delirium reported significantly more long-term problems with memory and concentration after ICU discharge than before when compared with nondelirium patients (Table 3).

Table 3 **Results of Short Form-36, Checklist Individual Strength-fatigue, and the Cognitive Failure Questionnaire measurements 18 months after ICU discharge adjusted for covariates**

	Nondelirium Patients (n=744)		Delirium Patients (n=171)		*P*[a]	General Population Subgroup Age **55-64y** (21)
Short-Form-36						
Physical Functioning	75	[50-90]	55	[25-80]	.18	72±26
Role-Physical	50	[0-100]	25	[0-75]	.20	67±41
Bodily Pain	78	[57-100]	78	[55-100]	.26	71±25 62±20
General Health	60	[40-75]	55	[35-70]	.90	82±23
Social Functioning	88	[63-100]	75	[50-88]	.65	68±20 81±35
Vitality	60	[45-75]	55	[40-75]	.94	77±18
Role-Emotional	100	[33-100]	100	[22-100]	.64	50±9 52±10
Mental Health	80	[64-92]	72	[60-88]	.26	
Physical Component Score	44	[35-52]	38	31-48]	.66	
Mental Component Score	53	[43-58]	50	[38-57]	.61	
Checklist individual strength-total	28	[17-39]	32	[22-44]	.13	
Cognitive Failure Questionnaire						
Memory	7.0	[4-10]	8.0	[5-12]	.08	
Distractibility	11.0	[6-15]	11.0	[7-16]	.19	
Social blunders	6.0	[4-9]	8.0	[4-10]	.04*	
Names	3.0	[2-4]	3.0	[2-4]	.22	
CFQ-total	26	[17-35]	28	[19-39]	.03*	

Data are expressed as median with interquartile range or mean with SD (±)
[a] Adjusted for gender, urgent admission, Acute Physiology and Chronic Health Evaluation-II score, sepsis and length of stay-intensive care unit using log transformed data (not shown); [b] < .05

Duration of delirium and HRQoL

The median duration of delirium was 2 days (interquartile range 1-7, range 1-69 days). The delirium duration was significantly correlated with the dimensions 'memory' (r = .21; p = .01) and 'names' (r = .18; p = .04) of the CFQ. This indicates that a longer duration of delirium is related to more pronounced problems in memory and remembering names. No other statistically significant correlations between duration of delirium and the dimensions of the SF-36 and CIS-fatigue were found.

Differences in HRQoL between subtypes of delirium

There were no differences between the subgroups of delirium concerning age, Acute Physiology and Chronic Health Evaluation-II score, gender and sepsis.

However, there were significant differences between the delirium subtypes on admission type, admission to the ICU for urgent reasons, ICU and in-hospital length of stay (Table 4). These variables were considered as covariates. In the unadjusted database, survivors of a hypoactive delirium subtype evaluated their HRQoL on several dimensions higher compared with hyperactive and mixed delirium survivors. After adjusting for the covariates patients who had a hypoactive delirium evaluated their mental health significantly better than those who suffered from a mixed or hyperactive delirium subtype (p = .01 and p = .04, respectively).

We found no other significant differences in the SF-36, CIS-fatigue and CFQ tests between the subtypes of delirium. Taken together, the three subgroups of delirium suffered more extensive cognitive impairment compared to the patients without delirium during their ICU stay.

Table 4 **Differences between subtypes of delirium on Health Related Quality of Life scores**

	Hypoactive subtype (n=63)	Hyperactive subtype (n=19)	Mixed subtype (n=89)
Age	68 [59-75]	64 [57-75]	64 [57-75]
Gender (male)	36 (57%)	10 (53%)	55 (62%)
Acute Physiology and Chronic Health Evaluation-II score	16 [14-21]	14 [13-18]	17 [15-21]
Urgent admission (N)	43 (68%)	9 (47%)	76 (85%) [a,b]
Length of stay-intensive care unit (days)	4 [2-7]	3 [1-6]	8 [3-16][a,b]
Length of stay-hospital (days)	15 [7-29]	10 [5-20]	24 [12-24][a,b]
Sepsis (n)	3 (5%)	1 (5%)	12 (14%)
Admission type			
- Surgical	29 (46%)	14 (74%)[a]	(38%)[a,b]
- Medical	21 (33%)	3 (16%)[a]	30 (34%)[b]
- Trauma	4 (6%)	2 (11%)[a]	11 (12%)
- Neurology/Neurosurgical	9 (14%)	0 (0%) [a]	14 (16%)[b]
Short Form-36[d]			
Physical Functioning	66 [35-85]	32 [15-71]	50 [30-75]
Role-Physical	50 [0-100]	38 [0-100]	25 [0-63]
Bodily Pain	78 [67-100]	57 [32-100]	78 [55-100]
General Health	56 [38-70]	48 [19-65]	50 [35-65]
Social Functioning	75 [63-100]	63 [34-90]	69 [50-88]
Vitality	58 [45-76]	50 [35-60]	55 [40-70]
Role-Emotional	100 [33-100]	83 [17-100]	100 [0-100]
Mental Health	80 [65-92][a-c]	64 [56-84]	72 [52-84]
Physical Component Score	37 [22-48]	41 [33-49]	36 [29-45]
Mental Component Score	48 [33-56]	52 [41-59]	49 [37-57]
Checklist individual strength [d]			
-total	30 [16-44]	33 [26-48]	33 [23-44]
Cognitive Failure Questionnaire [d]			
Memory	9 [5-12]	8 [5-13]	8 [5-12]
Distractibility	11 [7-16]	11 [6-16]	11 [7-16]
Social blunders	8 [4-9]	5 [2-11]	8 [5-11]
Names	3 [2-4]	4 [3-5]	3 [2-4]
CFQ-total	29 [20-37]	25 [17-39]	29 [19-42]

[a] Significant difference between hypoactive and hyperactive subtype; [b] Significant difference between hypoactive and mixed type subtype; [c] Significant difference between hyperactive and mixed type subtype; [d] adjusted for urgent, length of stay-ICU and in-hospital, and admission type using log transformed data (data not shown)

Discussion and conclusion

We demonstrated that median 18 months after ICU discharge there was no difference between patients with delirium and nondelirium patients on all domains of the SF-36 and the CIS-fatigue, adjusted for relevant covariates. However, patients who suffered from delirium during their ICU stay experienced significantly more cognitive problems than those who did not, even after adjusting for covariates. Furthermore, delirium duration was significantly correlated to problems with memory and names. Interestingly, after adjusting for relevant covariates, survivors with a hyperactive or mixed subtype of delirium qualified their mental health on the SF-36 as significantly worse than the hypoactive delirium patients.

Delirium is recognized as a frequent disorder with serious short-term health related problems and is associated with longer hospital length of stay and increased mortality rates (5;27-30). Furthermore, in long-term studies it is recognized that hospitalized, non-ICU, patients with delirium suffer from persistent cognitive impairment (31;32). Also, ICU patients suffer from persistent cognitive impairment during long-term follow-up (7;33;34), but in these studies no distinction between delirious and nondelirious patients was made. A long-term ICU study that distinguished between delirious and non-delirious patients showed that, in addition to role functioning, there was no statistically significant difference between either group (13) while in another long-term study it was observed that duration of delirium was independently associated with more pronounced cognitive impairment (6). Definite conclusions cannot be drawn from these relatively small studies, because they used a more restricted HRQoL survey (13), their maximum follow-up duration was 12 months (6;13), they mainly focused upon cognitive impairment (6) and made no adjustments for relevant covariates (13). This last point is of particular concern as more severely ill patients have a higher incidence of delirium and long-term impairments which may not be related to each other (27).

The strength of the present study is that we used a set of validated questionnaires, such as the SF-36, which is the preferred choice for the post-ICU setting (20). In addition, because of the large sample size we were able to correct for covariates and the longer follow-up emphasizes the clinical relevance of the observations.

Overall and consistently, each group of delirium subtype evaluated their cognitive functioning lower than the patients who did not suffer from delirium during their ICU stay. In our study we found that patients who suffered from a hypoactive delirium evaluated their HRQoL on several domains of the SF-36 as less affected than the hyperactive or mixed subtype delirium patients. After adjusting for relevant covariates the domain mental health remained significantly better in hypoactive delirium survivors. The hypoactive subtype is associated with a higher mortality

rate (35;36), a finding that we confirmed in our study and this may have biased the results to some extent.

Our findings of prolonged cognitive impairment in ICU survivors who suffered from delirium corroborate the results of a recent meta-analysis that showed that hospitalized (non-ICU) patients with delirium have a significantly increased risk of developing dementia (37). Our results that duration of delirium correlates with prolonged cognitive problems further extends the reported effects in 77 patients 12 months after their ICU stay (6) and illustrates its clinical importance. This may indicate that interventions aimed at reducing delirium incidence and/or shortening its duration may produce long-term beneficial effects. This has not been studied yet.

We wish to acknowledge several study limitations. Firstly, it is intrinsic to long-term research in this patient group that the most severely ill may not be alive 18 months after their ICU discharge. As the occurrence and duration of delirium is related to increased mortality (27;29;38) and the cognitive impairments recover in time (6) this may result in an underestimation of the effects of delirium on cognitive impairment in a long-term study such as ours. This implies that the correlation between duration of delirium and HRQoL and cognitive impairment could be underestimated in our population. Secondly, we diagnosed delirium on minimal one positive CAM-ICU screening during patients' ICU stay. One could argue that it is better to use at least two consecutive positive CAM-ICU screenings to diagnose delirium. However, in all guidelines and delirium protocols we are aware of, patients are treated when they meet the criteria of delirium. This is the case following one positive CAM-ICU screening. According to our intensive care delirium protocol patients are treated with haloperidol when a patient has at least one positive CAM-ICU screening. This early treatment with haloperidol may result in negative following CAM-ICU's. Therefore, to include patients with two or more positive CAM-ICU scores may underestimate the presence of delirium in successfully treated patients (with haloperidol). To not recognize these patients as delirium patients is, in our opinion, not correct and not in line with daily practice. In addition, in total only seven out of the 171 responding patients with a delirium had only one positive CAM-ICU screening and they were all treated with haloperidol following the first positive CAM-ICU. These were all patients with a hyperactive delirium subtype. The results of our study would not be influenced if these seven patients would not be included. Thirdly, we adjusted for significant differences in demographic variables between nondelirium and delirium patients. As delirium is an independent predictor of longer ICU length of stay (27), presumably independent of severity of illness, then adjustment for ICU length of stay in the analyses relating delirium to long-term outcomes may underestimate the long-term effects of delirium. Furthermore, we measured patients' long-term evaluation on HRQoL after ICU discharge once only. This can be considered as a

limitation as we do not know how patients' QoL developed during these 18 months. It appears plausible that the results would have been different when we would have also measured them in an earlier stage after discharge. Khouli et al (39) showed that a higher proportion of older patients died within 6 months after ICU discharge and the HRQoL worsened after 6 months in the oldest group but improved in the younger group. However, taking into account the fact that cognitive impairment improved in delirium patients between 3 and 12 months after ICU discharge (6), differences between the delirium and nondelirium ICU survivors in our group was probably more pronounced earlier in the course of recovery. Since the aim of our study was to examine the long-term effects of delirium, we decided not to conduct repeated measures of the HRQoL status in a smaller group of patients, instead we chose to measure one point in time, after 18 months, in a large group of patients. This allowed adjustment for relevant covariates.

In conclusion, in this large and long-term follow-up study we demonstrated that ICU survivors with delirium during their ICU stay had a similar adjusted health related quality of life evaluation, but experienced significantly more cognitive problems in comparison to those who did not suffer from delirium. Furthermore, the duration of delirium is related to long-term cognitive problems.

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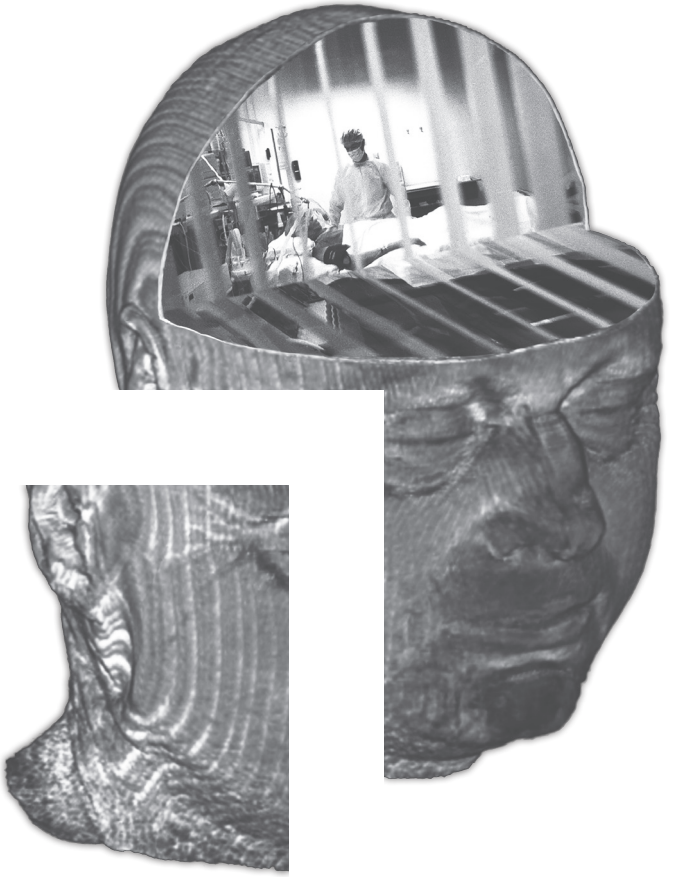

PART THREE

Prediction and Prevention of Delirium in Intensive Care Patients

8

PRE-DELIRIC, PREdiction of DELIRium in ICu patients; Development and Validation of a Delirium Prediction Model for Intensive Care Patients

Mark van den Boogaard, Peter Pickkers, Arjen J.C. Slooter, Michael A. Kuiper, Peter E. Spronk, Peter H.J. van der Voort, Johannes G. van der Hoeven, Rogier Donders, Theo van Achterberg, Lisette Schoonhoven

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Abstract

Objectives

While delirium is a serious and frequent disorder in intensive care patients, a prediction model is currently not available. We developed and validated a delirium prediction model for adult intensive care patients and determined its additional value compared to the prediction of the caregivers.

Design

Observational multicenter study.

Setting

Five intensive care units in the Netherlands (two University hospitals and three University-affiliated teaching hospitals).

Participants

3,056 intensive care patients aged ≥18 years.

Main outcome measures

The main outcome was the development of delirium during patient stay in the intensive care. Delirium was defined as minimal one positive delirium screening during patients' intensive care stay.

Methods

Two independent cohort studies were performed in one hospital to develop and temporally validate the model. All admitted adult ICU patients were screened for delirium and 25 potentially important risk factors were collected within 24 hours after intensive care admission. Data of four other hospitals were used for external validation. In a subgroup, caregivers were asked to predict whether or not the patient would develop delirium during their intensive care stay.

Results

We included 1,613 and 549 consecutive intensive care patients to develop and temporally validate the model. For external validation data of 894 patients were collected. The prediction (PRE-DELIRIC) model contains 10 risk factors; i.e. age, APACHE-II, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, urea level and urgent admission. The model had an area under the receiver-operating-characteristic (AUROC) of 0.87 (95%CI 0.85 to 0.89) and 0.86 after bootstrapping. Temporal validation and external validation resulted in AUROC's of 0.89 (95%CI 0.86 to 0.92) and 0.84 (95%CI 0.82 to 0.87), respectively. The pooled AUROC (N=3056) was 0.85 (95%CI 0.84 to 0.87). The AUROC of nurses' and physicians' prediction (N=124) was significantly lower, both 0.59 (95%CI 0.49 to 0.70).

Conclusion

The PRE-DELIRIC model for intensive care patients consists of 10 risk factors that are readily available within 24 hours after intensive care admission and has a high predictive value. The clinical prediction of nurses and physicians performed significantly worse. The model allows for early delirium prediction and the initiation of preventive measures.

INTRODUCTION

Delirium, characterized by an acute onset of fluctuating changes in mental status and changed levels of consciousness and inattentiveness,(1) has a high incidence rate in critically ill patients (2-4). It is a serious disorder associated with a prolonged intensive care unit and in-hospital stay, higher costs and increased morbidity and mortality rates (2;3;5).

There are several delirium assessment tools for intensive care patients of which the confusion assessment method–intensive care unit (CAM-ICU) has the highest sensitivity and specificity (6;7). It is important that intensive care patients are screened (8-10) in order to provide timely treatment. However, preventive measures for delirium may also reduce its incidence, severity and duration as determined in other patient groups (11;12). General preventive measures in all intensive care patients is time consuming and may expose a substantial number of patients to unnecessary risks, for example the side-effects of pharmacological prophylaxis. Whilst several predictive models for non-intensive care patients exist (13;14) and one for the older medical intensive care patient (15), currently no evidence-based prediction model for general intensive care patients is available. In addition, we wished to determine whether or not the model had additional value compared to the prediction of the caregivers.

Objective

The aim of our study was to develop and validate a delirium prediction model for intensive care patients and to determine its value compared to the prediction of the attending nurses and physicians.

Methods

Study design

Observational multicenter study in which first the PREdiction of DELIRium for Intensive Care patients (PRE-DELIRIC) model was developed and on a second prospective cohort the model was temporally validated in the same hospital. The model was then validated externally in four other Dutch hospitals.

Development and temporal validation of the model

To develop the prediction model a prospective cohort study was carried out in the Radboud University Nijmegen Medical Centre, the Netherlands. This study was conducted between February 1, 2008 and February 1, 2009.

A second prospective cohort study was carried out in the same hospital for temporal validation (16) of the model and was conducted between May 1, and September 1, 2009.

External validation

After development and temporal validation the delirium prediction model was externally validated with data of intensive care patients admitted to four other Dutch hospitals between January 1 and September 1, 2009.

Table 1 Characteristics of participating hospitals

Participating Hospitals	ICU-beds for adults (annually admissions)	Type of ICU-population	Implementation CAM-ICU	CAM-ICU screening
Radboud University Nijmegen Medical Centre, Nijmegen[1]	33 beds (2000-2500)	Medicine, surgery, neurocritical care and cardiothoracic surgery	- year: 2007 - type of training: group and individual training	- 3/daily - Compliance rate 90.4% - IRR >0.8
University Medical Centre Utrecht, Utrecht[1]	32 beds (2000-2500)	Medicine, surgery, neurocritical care and cardiothoracic surgery	- year: 2007 - type of training: group and individual training	- 2/daily - Compliance and IRR: NM
Medical Centre Leeuwarden, Leeuwarden[2]	16 beds (1400-1500)	Medicine, surgery and cardiothoracic surgery	- year: 2008 - type of training: group and individual training	- 3/daily - Compliance rate 90% - IRR:NM
Gelre Hospital, Apeldoorn[2]	10 beds (600)	Medicine and Surgery	- year: 2004 - type of training: group and individual training	- 3/daily - Compliance rate 90% - IRR: NM
Onze Lieve Vrouwe Gasthuis, Amsterdam[2]	18 beds (1500-1800)	Medicine, surgery and cardiothoracic surgery	- year: 2006 - type of training: group and individual training	- 3/daily - Compliance rate 96.2% - IRR: NM

[1] University hospital, [2] University-affiliated teaching hospital
IRR: Interrater reliability expressed in Cohen's kappa, NM: not measured

One of these hospitals was a university hospital and three were university-affiliated teaching hospitals, all with mixed intensive care populations (Table 1). In these hospitals, the CAM-ICU was performed at least twice daily by trained intensive care nurses.

Delirium prediction of caregivers

To compare the predictive value of the model with that of the caregivers, within 24 hours after intensive care admission, intensive care nurses and physicians caring for the patient independently were asked to predict if the patient would develop a delirious period during their complete intensive care stay.

Study population for the development and validation studies

After the successful implementation of the validated Dutch version of the CAM-ICU,(17) the interrater reliability of the delirium screenings of the intensive care nurses was above 0.80 Cohen's kappa, with a compliance rate of over 90%, as described in more detail previously (10). During the development and temporal validation studies all adult patients admitted to the intensive care were included. In order to detect delirium, all consecutive adult intensive care patients were screened by the intensive care nurses at least three times daily, and more often if required, for example following sudden changes in behaviour, attention or consciousness. This screening frequency was in accordance with screening in daily practice. Patients were excluded if: they were delirious within 24 hours after intensive care admission; had a sustained Richmond agitation sedation score (RASS) of -4/-5 during complete intensive care admission; stayed on the intensive care for less than one day; had serious auditory or visual disorders; were unable to understand Dutch; were severely mentally disabled; suffered from a serious receptive aphasia or if the compliance rate of the delirium screening was <80% during a patients' stay in the intensive care.

In order to meet the same inclusion and exclusion criteria during the external validation study consecutive patients with complete CAM-ICU screenings, defined as CAM-ICU compliance rate >80% per patient, were used. Patients were diagnosed as having a delirium when they had at least one positive CAM-ICU screening during their intensive care stay or were treated with haloperidol, since in these hospitals haloperidol is only used for delirium treatment. To examine the predictive value of the PRE-DELIRIC model in daily practice in these hospitals, no compliance and interrater reliability measurements were performed and only data of CAM-ICU screenings as performed in normal daily practice were used.

Potential predictors

Demographic variables and information on potential risk factors identified by a recent systematic review (18) were collected electronically within 24 hours of intensive care admission (see appendix A, *electronic supplement*). In addition, we included variables from the Dutch National Intensive Care Evaluation database (19) as potential risk factors when the delirium incidence rate associated with that

variable was >50% higher than the incidence rate of the total group (see appendix B, *electronic supplement*). Wherever possible, the risk factors were collected as continuous variables (categorical or dichotomized when otherwise).

Outcome definition

In view of the study aim to develop and validate a delirium prediction model the main outcome measure was delirium development during patient stay in the intensive care. Delirium was defined as a minimum of one positive CAM-ICU screening during each patient's intensive care stay. In addition, medical and nursing files of patients were screened daily for signs of delirium (20). If the files provided signs of delirium without a positive CAM-ICU screening or conversely, if the files did not provide evidence of delirium and there was a positive CAM-ICU result, patients were additionally screened by a delirium expert according to the DSM-IV criteria (1) to rule out false negatives and false positives.

Data management and quality checks for the development and temporal validation studies

The performance of CAM-ICU screenings was monitored to ensure the quality of data collection. Compliance was calculated as the percentage of assessments performed per day in relation to the total number of assessments that should have been performed. The mean compliance during the development and temporal validation studies was 90.4%. The quality of the CAM-ICU performance was measured as the interrater reliability. For this, the CAM-ICU screening assessed by the attending intensive care nurse was compared with the CAM-ICU score assessed by an expert psychiatry nurse within a time-window of one hour. 120 interrater reliability measurements were randomly performed resulting in a Cohen's kappa of 0.90 (95%CI 0.82 to 0.98). The data of 15% of all patients included were randomly double checked by the first author for completeness and accuracy.

The regional Medical Ethical Committee approved the study and waived the need for informed consent, since no additional interventions were carried out and data collection was not burdensome to patients.

The development and validation studies were registered in the Clinical trial register as NCT00604773 and NCT00961389, respectively.

Statistical analysis

The sample size needed for the development of the model was calculated based on the need of 10-15 delirious patients per risk factor plus 10% drop-outs. Missing data concerning the risk factors were imputed. Missing values during the development study were urea (0.7%), liver enzymes (3.0%), bilirubin (18.0%), calcium (4.5%),

sodium (0.3%), hematocrit (0.4%), metabolic acidosis (1.0%), Acute Physiology and Chronic Health Evaluation (APACHE)-II scores 0.7%. Data for all other variables were complete. All data of the temporal validation study were complete. We decided that if a laboratory measurement was not determined, there was no reason to assume that the missing variable had an abnormal value, and imputed the mean normal value. To calculate the normal value we first select all patients with a normal value and then the mean value was calculated of these group of patients and used for imputation. When the APACHE-II score was missing we imputed the mean value of the variable of the delirium or non-delirium group, depending on the results of the CAM-ICU. In the external validation data set 6.3% of the urea values were missing and imputed. Concerning the APACHE-II, 0.6% of the scores were missing and a mean APACHE-II score of the group was imputed in the external validation set.

Univariate logistic regression was used to develop the prediction model by assessing the association between each potential prognostic determinant and the presence and absence of delirium. Determinants with a p value > .15 in univariate analysis or with a prevalence rate <10%, were excluded. With the remaining risk factors, multivariate logistic regression analysis with backward elimination (excluding risk factors with p values > .10) was used to evaluate the independent associations with the occurrence of delirium. The final model therefore contains independent risk factors for delirium. The prognostic ability to discriminate between patients with and without delirium was estimated using the area under the receiver operating characteristic curve (AUROC). Bootstrapping techniques were used to adjust for overfitting, i.e. for overly optimistic estimates of the regression coefficients of the risk factors in the final model. Two hundred random bootstrap samples resulted in shrunken regression coefficients of the risk factors and area under the curve(21) of the developed model.

In both validation studies shrunken regression coefficients of each risk factor were multiplied by the observed patients' value. The outcome is a calculated predicted probability on which a new AUROC was built. Finally, to examine how well the model was calibrated, linear predictor values were calculated for each patient of every one cohort using the coefficients from the final development model. These linear predictors were used in a logistic regression model to test whether the prediction rule was well calibrated resulting in a calibration slope and an intercept. A calibration slope of '1' and an intercept of '0' demonstrates a perfect calibration. Calibration plots of each cohort are available in the electronical supplement Appendix D.

Statistical analysis were performed using Statistical Package for Social Sciences (SPSS®) 16.01, R statistics version 2.10.1(22) using the rms package.(23)

Results

Development of prediction model

In total 2,116 consecutive patients were screened of which 503 were excluded (Figure 1). Out of the remaining 1,613 patients, 411 (25.5%) developed delirium. Patient characteristics are shown in Table 2 and prevalence rates and delirium incidence rates for the separate risk factors are shown in the *electronical supplement* Appendix B and Appendix C. Of the 25 potential risk factors we excluded alcohol abuse (7.8%), dementia (1.7%), use of an epidural catheter (2.2%), hyperamylasemie (3.9%), hyponatriemia (5.8%), use of dopamine (0.2%) and use of lorazepam (0.7%) because of a prevalence rate below 10%. Hypertension was excluded because of P-value >0.15 in univariate logistic regression analysis. After multivariate logistic regression analysis with the remaining risk factors, we constructed the PRE-DELIRIC model which consisted of ten risk factors (Table 3). The AUROC was 0.87 (95%CI 0.85 to 0.89) and 0.86 after bootstrapping. Calibration of the model resulted in an calibration slope of 1.08 and an intercept of -0.06.

Temporal validation of prediction model

In the prospective validation study, 748 consecutive patients were screened of which 199 patients were excluded (Figure 1). Out of the remaining 549 patients, 171 (31.1%) patients developed delirium (Table 2). The temporal validation resulted in an AUROC of 0.89 (95%CI 0.86 to 0.92). The calibration slope of the temporal model was 1.2 and the intercept 0.22.

External validation of the prediction model

Data of 894 non-selected intensive care patients (Table 2) were used for external validation resulting in an AUROC of 0.84 (95%CI 0.82 to 0.87) with a calibration slope of 0.76 and an intercept of -0.59. The AUROCs of the four different hospitals did not differ from each other (data not shown).

Table 2 Patient characteristics of the cohort studies

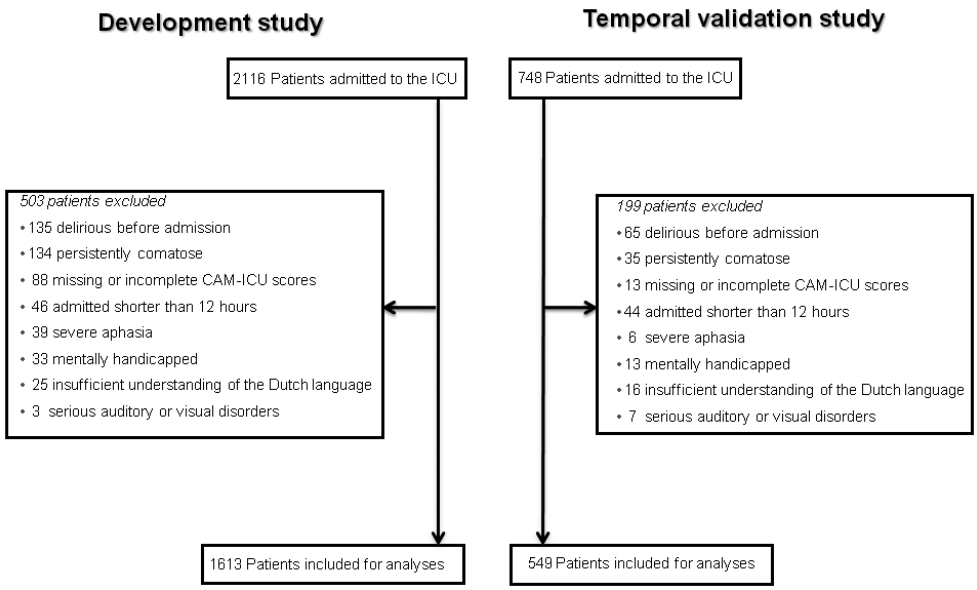
Variable	Development study (N=1613)	Temporal validation study (N=549)	External validation study (N=894)	All included patients (N=3056)
Age mean in y median [IQR, range]	64 [54-72, 76]	64 [54-73, 72]	67 [58-75, 78]	65 [55-73, 78]
Male (%)	1027 (63.7)	353 (64.3)	557 (62.3)	1937 (63.4)
APACHE-II score median [IQR, range]	14 [11-18, 41]	15 [11-18, 47]	16 [13-21, 44]	15 [12-19, 48]
Delirium (%)	411 (25.5)	171 (31.1)	329 (36.8)	911 (29.8)
Days till onset delirium in days median[IQR, range]	2 [2-5, 53]	2 [2-5, 44]	N.A.	N.A.
Urgent admission (%)	852 (52.8)	232 (42.3)	495 (55.4)	1579 (51.7)
Mechanically ventilated (%)	78.5%	87.1%	89.6%	83.7%
Sedation (%)	386 (23.9)	184 (33.5)	543 (60.7)	1113 (36.4%)
LOS-ICU, in days median [IQR, range]	2 [2-4, 118]	2 [2-4, 69]	4 [2-8, 100]	3 [2-7, 118]
LOS-in hospital in days median [IQR, range]	9 [5-19, 247]	9 [5-15, 98]	10 [6-20, 88]	10 [5-19, 249]
Admission category (%)				
1. Surgery	1010 (62.6)	340 (61.9)	507 (57.0)	1857 (60.8)
2. Medical	360 (22.3)	123 (22.4)	297 (33.2)	780 (25.5)
3. Trauma	80 (5)	18 (3.3)	30 (3.4)	128 (4.2)
4. Neurology/ neurosurgery	163 (10.1)	68 (12.4)	60 (6.7)	291 (9.5)

Data are presented as mean (SD, with range), unless mentioned otherwise

As there were no differences in prediction between the three studies we pooled the data (N=3056) resulting in an AUROC of 0.85 (95%CI 0.84 to 0.87) (Figure 2). The pooled data resulted in an overall calibration slope of 0.93 with an intercept of -0.29 indicating a good calibration.

We divided the complete group in four different risk groups; low, moderate, high and very high risk group with a cut of value 20%, 40%, 60% and >60%, respectively. Sensitivity, specificity and likelihood ratios per risk group are expressed in Figure 2. The calibration plot of the pooled data is depicted in Figure 3.

Figure 1 **Study flow chart of the development and temporal validation study**



Delirium prediction of caregivers

In a convenience sample of 124 patients, attending intensive care nurses and physicians were asked to predict delirium independently of each other, similar to the prediction model 24 hours within intensive care admission. The AUROC of the prediction of the nurses (AUROC 0.59; 95%CI 0.49 to 0.70) and physicians (AUROC 0.59; 95%CI 0.49 to 0.70) was inferior compared with the predictive value of the PRE-DELIRIC (AUROC 0.87; 95%CI 0.81 to 0.93) in this specific subgroup of 124 patients. There were no significant differences between the prediction made by intensive care nurses (75%) and student intensive care nurses (25%) and between predictions made by intensivists (36%), fellow-intensivists (40%) and residents (24%) predictions (data not shown).

Table 3 **Variables of the PRE-DELIRIC model and regression coefficients**

Variable	Regression coefficient	Odds ratio (95%-CI)	Shrunken regression coefficient
1. Age (y)	0.04	1.04 (1.03 to 1.06)	0.04
2. APACHE-II score (per point)	0.06	1.06 (1.03 to 2.0)	0.06
3. Coma			
1. Medication induced	0.59	1.8 (1.1 to 3.1)	0.55
2. Miscellaneous	2.92	18.5 (4.6 to 73.8)	2.70
3. Combination	3.06	21.3 (5.9 to 77.1)	2.84
4. Admission category			
1. Surgery	RC	RC	RC
2. Medical	0.33	1.4 (0.9 to 2.2)	0.31
3. Trauma	1.22	3.4 (1.7 to 6.8)	1.13
4. Neurology/ neurosurgery	1.49	4.5 (2.6 to 7.5)	1.38
5. Infection (yes)	1.14	3.1 (2.0 to 4.8)	1.05
6. Metabolic acidosis (yes)	0.32	1.4 (1.0 to 2.0)	0.29
7. Morphine use			
1. 0.01-7.1mg/day	0.44	1.6 (0.8 to 3.1)	0.41
2. 7.2-18.6mg/day	0.14	1.2 (0.8 to 1.8)	0.13
3. >18.6mg/day	0.55	1.8 (1.1 to 2.7)	0.51
8. Sedation (yes)	1.51	4.5 (2.8 to 7.4)	1.39
9. Urea (mmol/L)	0.03	1.03 (1.0 to 1.1)	0.03
10. Urgent admission (%)	0.43	1.5 (1.1 to 2.3)	0.40
Intercept	-6.76		-6.31

RC= reference category. Shrunken regression coefficients are a result of the used bootstrapping technique to correct for over optimistic estimation of the model.

The formula of the PRE-DELIRIC model is:

Risk of delirium = 1/(1+exp- (-6.31

+0.04 x age

+ 0.06 x *APACHE-II score*

+ 0 for non coma or 0.55 for *medication induced coma* or 2.70 for *miscellaneous coma or 2.84 for combination coma*

+ 0 for surgical patients or 0.31 medical patients or 1.13 for *trauma* patients or 1.38 for *neurology/neurosurgical* patients

+ 1.05 for *infection*

+ 0.29 for metabolic acidosis

+ 0 for non morphine use or 0.41 for *0.01-7.1mg*/24hours morphine use or 0.13 for 7.2-18.6mg/24hours morphine use or 0.51 for *>18.6mg*/24hours morphine use

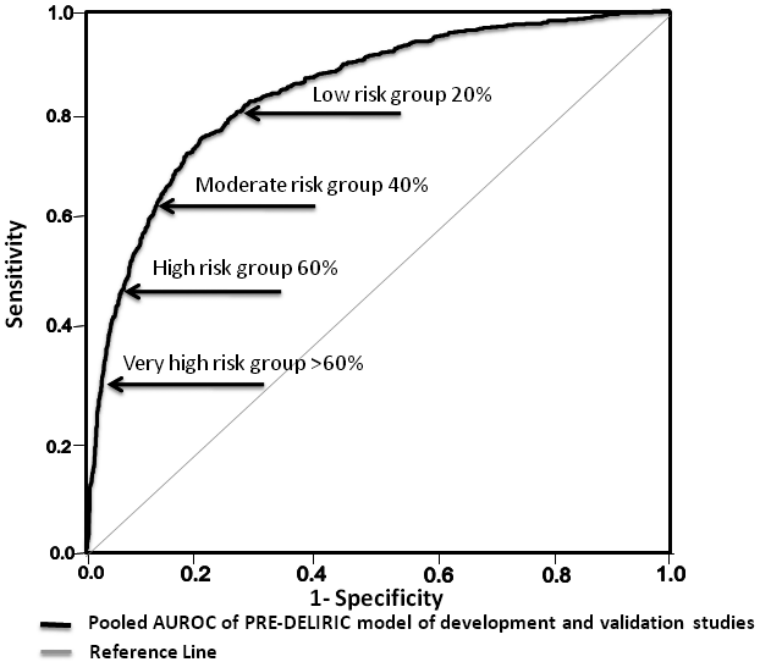
+ 1.39 for *use of sedatives*

+ 0.03 x *urea level* (mmol/L)

+ 0.40 for *urgent admission*))

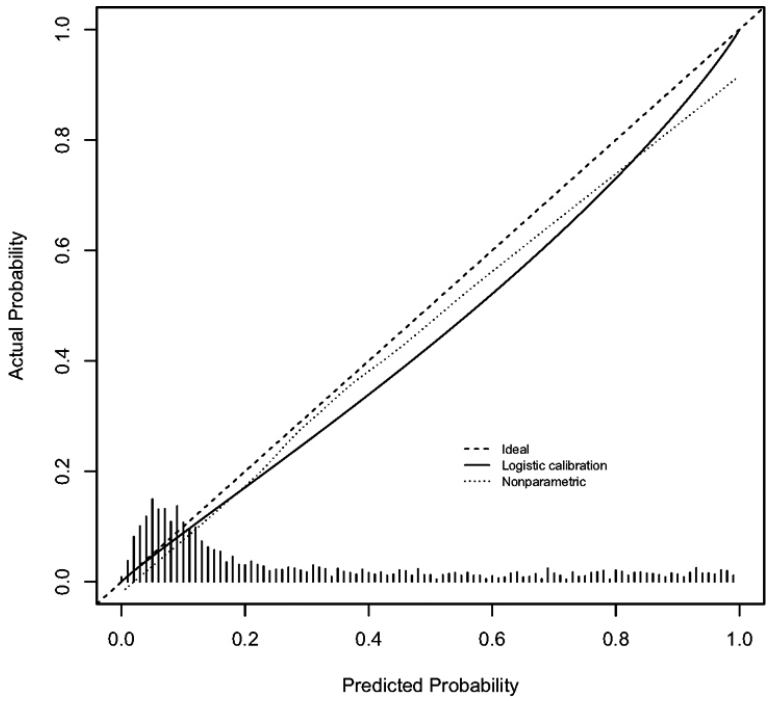
The scoring system's intercept is expressed as -6.31 represents, the other numbers represent the shrunken regression coefficients (weight) of each risk factor.

Figure 2 **Area under the receiver-operating-characteristic of pooled data of the development (AUROC 0.86), the temporal validation (AUROC 0.89) and external validation (AUROC 0.84) resulting in an AUROC of 0.85. The AUROC of the prediction of the nurses was 0.59 (95%CI 0.49 to 0.70) and physicians 0.59 (95%CI 0.49 to 0.70)**



	sensitivity	specificity	LR +	LR -
Low risk	80.7%	74.7%	3.19	0.26
Moderate risk	62.0%	88.8%	5.54	0.43
High risk	46.3%	94.6%	8.57	0.57
Very high risk	30.0%	97.7%	13.0	0.72

Figure 3 **Calibration plot of the pooled data with a calibration slope of 0.93 and an intercept of -0.29.**



Discussion

Principal findings

In this multicenter study we developed and validated a delirium prediction model for intensive care patients. To our knowledge, our study is the first delirium prediction study for general intensive care patients and represents by far the largest delirium-related study in intensive care patients to date. Our PRE-DELIRIC model reliably predicted the development of delirium for the complete length of ICU stay, based on ten readily available risk factors within 24 hours of intensive care admission. In addition, the AUROC of the PRE-DELIRIC model was significantly higher than the delirium prediction capacity of attending caregivers. These findings confirm that the model has additional value in daily practice. Importantly, dementia and alcohol abuse are not in the model since these patients need to be considered as high risk patients, irrespectively the presence of other risk factors.

Clinical relevance

The early prediction of delirium development in intensive care patients with the PRE-DELIRIC model facilitates the use of non-pharmacological preventive measures in high risk patients, such as improvement of orientation, cognitive stimulation, early mobilization(11) and music listening(24). In addition, it also facilitates pharmacological interventions in high risk patients such as the administration of prophylactic haloperidol (12). These interventions aim to improve patients' cognition or have a systemic effect, although the evidence of beneficial preventive measures of drugs (25) and nursing interventions in critically ill patients is limited at this moment. Non-pharmacological preventive measures were successful in reducing the incidence and duration of delirium in a non-critically ill hospital population with an intermediate to high risk for the development of delirium(11), while pharmacological prevention with haloperidol resulted reduced severity of delirium and delirium days, and a shorter hospital length of stay (12). Importantly, no data from ICU patients is available. Interestingly, early mobilization of mechanically ventilated intensive care patients results, besides other significant effects, resulted in a reduced duration of delirium (26).

The use of the PRE-DELIRIC model to identify and consequently preventively treat high risk patients could offer an important contribution to intensive care practice and efficient use of research resources to study only in high-risk patients. In addition, the modifiable risk factors of the model may facilitate the use of preventive measures. Currently, the PRE-DELIRIC model is used in clinical daily practice in the hospital that developed the model and intensive care patients with a high risk for delirium, ≥50% PRE-DELIRIC score, and patients with dementia or alcohol abuse, receive delirium preventive measures. Importantly, the optimal cut-off point of the PRE-DELIRIC-model and the most effective delirium preventive interventions for intensive care patients need to be studied in the near future.

Limitations of the study

Several limitations of our study should be addressed. First, although the CAM-ICU has a high sensitivity and specificity when used by dedicated research nurses,(27;28) recently the performance in daily practice used by bedside nurses proved to be lower (29). In this performance study, the CAM-ICU was measured at one point on one day, while our delirium diagnosis was based on all CAM-ICU screenings during patients' complete ICU stay, increasing the sensitivity of the test. In addition we also used haloperidol as a proxy for the delirium diagnose since in all participating centres haloperidol was only used to treat delirium and the hospitals with the highest CAM-ICU performance participated in the present delirium prediction study. In view of the fluctuating nature of delirium, all patients were screened three times

daily and more often if needed. When delirium was not detected with the CAM-ICU, but delirium was suspected based on medical and nursing reports, patients were additionally screened by a delirium expert according to the DSM-IV criteria (1). In addition, during the development and temporal validation study, we performed quality checks that demonstrated a high compliance rate and interrater reliability. We therefore presume that few patients were misdiagnosed.

Second, we used data of four other hospitals collected in the same study period. These centres implemented and clinically used the CAM-ICU combined with a delirium treatment protocol prior to the conduct of the present study. Regarding the external validation study, we only included patients with complete CAM-ICU screenings and patients who were treated with haloperidol for delirium. The case-mix of these patients showed a higher APACHE-II score, more sedated patients and more patients were admitted for medical reasons compared to the hospital were the primary development and validation studies were performed. These differences may explain the higher incidence rate of delirium in these hospitals. Because of logistic reasons and the fact we wanted to examine the predictive value of the PRE-DELIRIC model in daily intensive care practice, we did not perform quality checks such as interrater reliability measurements in these other hospitals. Despite these limitations, the PRE-DELERIC model showed a good predictive value in daily intensive care practice.

Third, as recommended (21), the risk factors used in our study were primarily based on a systematic review (18). Additional variables were included following the results of our first cohort. We added the 'diagnosis group', and 'urgent admission' as new risk factors because of a high delirium incidence rate associated with these items. While these variables were not found in the systematic review (18), some studies show that urgent admission to the intensive care and neurological conditions are risk factors for delirium (30;31). Our results of the development study demonstrate that these risk factors are of importance to predict delirium in intensive care patients. Because of a low prevalence rate, relevant risk factors such as hyponatraemia, alcohol abuse and dementia were excluded from the multivariate logistic regression analysis. The additional value of hyponatraemia for the model would be expected low since also the delirium incidence rate in patients with a hyponatraemia in the first 24 hours after intensive care admission is low. The importance of, e.g., dementia and alcohol abuse is recognized in several studies (4;32), and also in the present study their delirium incidence rate was high. In many institutes all these patients will receive preventive measures and therefore, physicians do not need a delirium prediction model in these specific subgroups. Moreover, adding these covariates to the model would decrease its sensitivity to the other covariates. For these reasons we did not include alcohol abuse and dementia in the PRE-DELERIC model.

Fourth, the negative likelihood ratio for patients with a predicted low chance to

develop delirium is relatively rather moderate. This indicates that in this group patients will develop delirium while they were classified as having a low risk. On the other hand, preventive measures are advised to be taken in patients with a high risk, and the higher the delirium risk the better the performance of the model. Nevertheless, it is important to realize that a predicted low risk does not exclude the possibility to develop delirium.

Finally, the PRE-DELIRIC model is a static model that yields a calculated probability for delirium 24 hours after ICU admission. Since the health status of a patient can improve or deteriorate during ICU stay, the probability of the development of delirium may also change. The present model does not take into account changes in health status. Despite this limitation of the PRE-DELIRIC model, the AUROC of the model is high. Still, it would be interesting to develop a dynamic prediction model using dynamic parameters, such as the sequential organ failure assessment (SOFA)-score, in order to improve its predictive value during the patients' stay on the ICU which may possibly also result in a better performance in the low risk group.

Conclusions and policy implications

In summary, using the PRE-DELIRIC model can predict delirium for the complete stay in the intensive care within 24 hours of admission. It is now possible to identify patients who have a high risk for developing delirium during their intensive care stay. This will facilitate identification of high risk patients and targeted initiation of preventive measures. Our study demonstrates that the use of the PRE-DELIRIC model is significantly better than the predictions of the attending caregivers and should therefore be used daily in intensive care practice.

An automatic version of the PRE-DELIRIC model (Excel and web based) can be downloaded at: http://www.umcn.nl/Research/Departments/intensive%20care/Pages/vandenBoogaard.aspx (English and Dutch version available)

Acknowledgement

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Appendix A supplement for web-only publication

Collected delirium predictors within 24 hours after intensive care admission

Variable	Category	Description
Age *(years)**	C	Continuous variable
Alcohol abuse*	D	Known medical history of alcohol abuse
Anaemia (*L/L*)*	C	Continuous variable of hematocrit, lowest value
APACHE-II score *(per point)**	C	Calculated 24 hours after ICU admission
Coma*	Cat	No coma: RASS-4/-5 maximum 8 hours RASS-4/-5 for longer than 8 hours: 1. With use of medication 2. Other (i.e. intra cerebral bleeding, post-resuscitation) 3. Combination (1+2)
Dementia*	D	Known medical history of dementia
Admission category#	Cat	1. Surgical 2. Medical 3. Trauma 4. Neurology/neurosurgical
Dopamine use*	D	Any use of dopamine
Elevated hepatic enzymes (ASAT and ALAT in *U/L*)*	C	Level of alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), highest absolute value
Epidural catheter*	D	Any use of an epidural catheter
Fever (in C^0)*	C	Continuous variable, highest absolute value
Hyperamylasemia (*U/L)*	C	Continuous variable, highest absolute value
Hyperbilirubinemia (*umol/*L)*	C	Continuous variable, highest absolute value
Hypertension*	B	Medical history of hypertension
Hypocalcaemia *(mmol/L)**	C	Continuous variable, lowest absolute value
Hyponatraemia *(mmol/L)**	C	Continuous variable, lowest absolute value
Hypotension*	B	Symptomatic, resulting in treatment, or systolic blood pressure < 80 mmHg
Infection*	D	Proven or strong suspicion of infection for which antibiotics were started
Lorazepam use*	D	Any use of lorazepam (oral or parenteral)
Metabolic acidosis*	B	pH <7.35 with bicarbonate <24mmol/L
Morphine use*	Cat	No morphine: no use of any morphine Cumulative use of any form of morphine: 1. 0.01-7.1mg 2. 7.2-18.6mg 3. 18.7-331.6mg
Respiratory disease*	D	Chronic obstructive pulmonary disease, cor pulmonale, pneumothorax, hematothorax, thorax trauma
Sedative use*	D	Any use of propofol, midazolam, lorazepam or combination
Urgent admission#	D	Unplanned intensive care admission
Urea *(mmol/L)**	C	Continuous variable, highest value in blood

C= continuously B=binary D=dichotomized Cat.=categorical
Risk factors based on systematic review or potential risk factors derived from Dutch National Intensive Care Evaluation database #*

Appendix B supplement for web-only publication

Prevalance rate of risk factors and delirium incidence rates in these group

Dichotomized variables	Percentage patients in development cohort (N=1613)	Delirium incidence rate in the specific group
Alcohol abuse	3.3% (53)	60.4% (32/53)**
Coma	20% (323)	69% (223/323)**
1. Medication	78.6% (253/323)	62.8% (159/253)
2. Miscellaneous	6.5% (21/323)	85.7% (18/21)
3. Combination	15.2% (49/323)	93.9% (46/49)
Dementia	0.5% (8)	87.5% (7/8)**
Admission category:		
1. Surgical	62.6% (1010)	15% (152/1010)
2. Medical	22.3% (360)	43.1% (155/360)**
3. Trauma	5% (80)	47.5% (38/80)**
4. Neurology/ neurosurgical	10.1% (163)	40% (66/163)**
Dopamine use	0.2% (3)	0% (0/3)
Epidural catheter	5.1% (83)	0.6% (9/83)
Hypertension	30.6% (494)	26.3% (130/494)
Infection	14.9% (241)	58.1% (140/241)**
Lorazepam use	0.6% (9)	33.3% (3/9)
Metabolic acidosis	18.2% (294)	58.8% (173/294)**
Morphine use:	54.8% (884)	19.7% (174/884)
1. 0.01-7.1mg/24hrs	8.5% (75)	1.6% (14/884)
2. 7.2-18.6mg/24hrs	63.1% (558)	8.1% (72/884)
3. 18.7-331.6mg/24hrs	28.4% (251)	10% (88/884)
Respiratory disease	31.5% (508)	37.8% (192/508)
Sedative use	23.9% (386)	62.4% (241/386)**
Urgent admission	52.8% (852)	38.3% (326/852)**

*** Delirium incidence rate for the variable was >50% higher than the incidence rate of the total group (=25.5%)*

Appendix C supplement for web-only publication

Prevalance of the PRE-DELIRIC risk factors in each cohort

Risk variable	Development study (N=1613)	Temporal validation study (N=549)	External validation study (N=894)
Age mean in y (SD)	62 (±15)	62 (±15)	65 (±14)
APACHE-II score (SD)	15 (±6)	15 (±6)	18 (±7)
Coma (%)			
1. Medication induced	253 (15.7)	82 (14.9)	273 (30.5)
2. Miscellaneous	21 (1.3)	7 (1.3)	8 (0.9)
3. Combination	49 (3.0)	40 (7.3)	58 (6.5)
Admission category (%)			
1. Surgery	1010 (62.6)	340 (61.9)	507 (57.0)
2. Medical	360 (22.3)	123 (22.4)	297 (33.2)
3. Trauma	80 (5)	18 (3.3)	30 (3.4)
4. Neurology/ neurosurgery	163 (10.1)	68 (12.4)	60 (6.7)
Infection (%)	241 (14.9)	70 (12.8)	245 (27.4)
Metabolic acidosis (%)	294 (18.2)	84 (15.3)	220 (24.6)
Morphine use			
1. 0.01-7.1mg/day	75 (4.6)	143 (26.0)	44 (4.9)
2. 7.2-18.6mg/day	558 (34.6)	147 (26.8)	24 (2.7)
3. >18.6mg/day	251 (15.6)	11 (2.0)	291 (32.6)
Sedation (%)	386 (23.9)	184 (33.5)	543 (60.7)
Urea (mmol/L) median [IQR]	7.0 [5.0-9.0]	7.6 [5.7-10.2]	7.5 [5.5-11.2]
Urgent admission (%)	852 (52.8)	232 (42.3)	495 (55.4)

Data are presented as mean (SD), unless mentioned otherwise

Appendix D supplement for web-only publication

Figure A Calibration plot of the development model

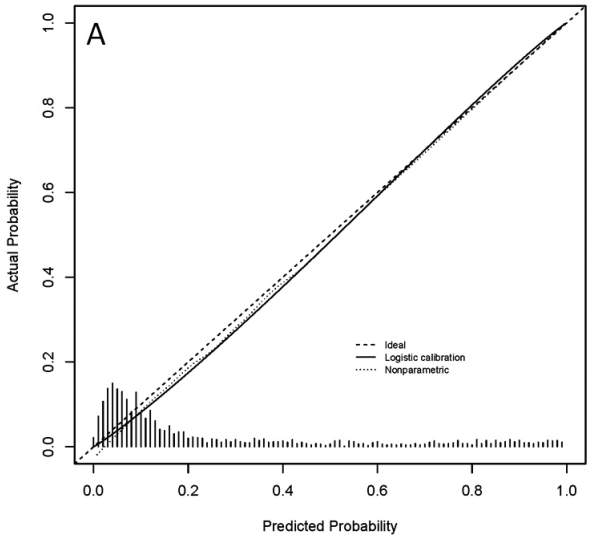


Figure B Calibration plot of the temporal validation model

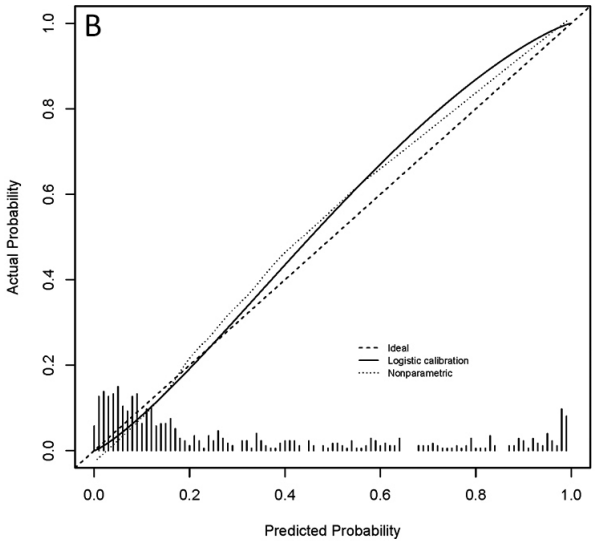
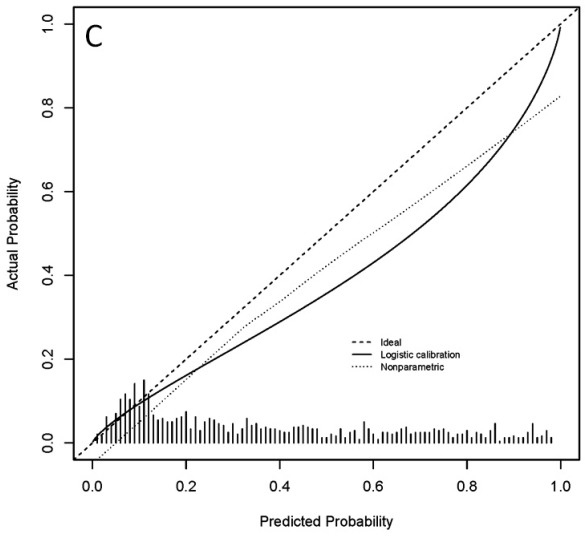


Figure C **Calibration plot of the external validation model**



9

Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium

Mark van den Boogaard, Lisette Schoonhoven,
Theo van Achterberg, Johannes G. van der Hoeven,
Peter Pickkers

Submitted

Abstract

Purpose

Delirium is a serious and frequent disorder but the effects of delirium prevention in intensive care (ICU) patients are unknown. We aimed to evaluate the effects of haloperidol prophylaxis in ICU patients with a high risk for delirium.

Methods

A prospective case-control study in 535 ICU patients with a predicted risk for delirium of ≥50%. Patients received haloperidol a 1mg/q/8 hours. Primary outcome were delirium incidence, delirium free days without coma and 28-day mortality. Results of prophylactic treatment were compared with a historical control group and a contemporary group that did not receive haloperidol prophylaxis.

Results

In 12 months 177 patients received haloperidol prophylaxis. Except for sepsis, patient characteristics were comparable between the prevention and the historical (*n*=299) group. Haloperidol prophylaxis resulted in a lower delirium incidence (65% vs. 75%, *p*=0.01), and more delirium-free-days (median 20 days [IQR 8-27] vs. median 13 days [3-27], *p*=0.003). Cox-regression analysis adjusted for sepsis showed an odds ratio of 0.80 (95%CI 0.66-0.98) for 28-day mortality. Furthermore, haloperidol prophylaxis resulted in less ICU re-admissions (18% vs. 11%, *p* = .03) and unplanned removal of tubes/lines (19% vs. 12%, *p* = .02). Haloperidol was stopped in 12 patients due to QTc-time prolongation (*n*=9), renal failure (*n*=1) or suspected neurological side-effects (*n*=2). No other side-effects were reported. Patients who were not treated during the intervention period (*n*=59) showed similar results compared to the untreated control group.

Conclusion

Haloperidol prophylaxis in patients with a high risk for delirium reduces delirium incidence, increases the number of delirium-free-days and reduces mortality rate.

Introduction

Delirium is a neuropsychiatric disorder characterized by an acute onset of confusion and consciousness alterations that fluctuate during the day (1). The incidence of delirium in intensive care (ICU) patients is high (2-5) and its presence is associated with prolonged duration of mechanical ventilation, increased ICU- and hospital length of stay (3;5), unplanned removal of tubes and catheters (5) and an increased mortality (5;6). Therefore, preventive treatment may be beneficial. In non-ICU patients beneficial effects of prophylactic haloperidol in older (7) and surgical patients (8) have been reported. A retrospective cohort study showed that ICU patients treated with haloperidol appear to have a lower mortality rate compared to non-treated ICU patients (9).

Preventive treatment of all ICU patients may attenuate the potential beneficial effects of haloperidol and would expose a substantial number of patients to unnecessary risks, for example the side-effects of haloperidol administration. With the use of a recently developed and validated delirium prediction model for ICU patients (10), patients with a high risk to develop delirium can be identified.

The aim of our present study was to evaluate the effects of prophylactic treatment with haloperidol in critically ill patients with a high risk for delirium.

Methods

Design and setting

A prospective case-control study carried out on the 33-beds intensive care unit (ICU) of the Radboud University Nijmegen Medical Centre, the Netherlands.

Delirium prevention

In August 2010 the delirium prevention policy was implemented in daily practice. Patients with an estimated risk of 50% or more determined with the delirium prediction model PRE-DELIRIC (10), and patients with a history of dementia or alcohol abuse were considered high risk. These high-risk patients received haloperidol 1 mg/8 hours or a lower dose of 0.5 mg/8 hours when they were ≥80years, had a body weight <50 kg, had a serum creatinine level >150 µmol/L or had serum bilirubin level >50 µmol/L. Prevention was not started when haloperidol was contra-indicated in case of Parkinson's disease, hypokinetic rigid syndrome, Lewis body dementia, prolonged QTc-time, pregnancy or in patients who were treated with other anti-psychotics. Patients who developed delirium were treated with therapeutic doses of haloperidol according to the department's protocol.

It was decided on beforehand to evaluate the effects of prophylactic use of haloperidol after 1 year and this evaluation study was registered in the Clinical trial register (NCT01187667).

Delirium assessment

All patients were screened by well-trained ICU nurses (11) using Dutch version of the CAM-ICU(12) at least three times daily, and more often if required. Patients were excluded in case of coma during complete ICU stay defined as sustained Richmond agitation sedation score (RASS) (13) of -4/-5, serious auditory or visual disorders, were unable to understand Dutch, severely mentally disabled or suffered from a receptive aphasia. Patients with delirium were divided in three subtypes (14): hyperactive (RASS +1/+4), hypoactive (RASS 0/-3), and mixed (RASS +4/-3). This last subtype of delirium is characterised by alternating symptoms of hyperactive and hypoactive delirium.

Patients were diagnosed with delirium when they had at least one positive CAM-ICU screening during their complete ICU stay. A delirium-and-coma-free day was defined as a negative CAM-ICU screening without RASS -4/-5 during a complete day. Follow-up of all patients was conducted prospectively.

Patients

Consecutive patients with a high risk for delirium admitted to our intensive care unit between August 1, 2010 and August 1, 2011 received haloperidol prophylaxis. To evaluate the effects of this prevention policy results were compared with a control group of high risk patients admitted between February 1, 2008 and February 1, 2009 and with a contemporary group of patients who did not receive prophylactic treatment for various reasons (Figure 1) during the prevention period.

Outcome measures

Primary outcome was; delirium incidence, number of delirium-free and coma-free days in 28 days, and 28-day mortality. Secondary outcomes were: duration of mechanical ventilation, incidence of re-intubation and re-admissions, incidence of unplanned removal of tubes/catheters and ICU- and hospital length of stay.

Statistical analyses

Demographic characteristics of patients who received haloperidol prophylaxis were compared with non-treated patients. Differences were tested depending on its distribution with Students T-test, Mann-Whitney U test or with the Chi-square test. Survival analyses with Kaplan-Meier curves as graphical presentation were used. To determine the effect of haloperidol on 28-day mortality adjusted for covariates we

used Cox-regression analysis with mortality as the dependent variable and baseline characteristics with a p-value <0.05 between groups as possible covariates. To examine which patients were most likely to benefit, we equally divided the total group in three risk groups (predicted risk up to 71%, between 71-89% and >89%). We also studied outcome in four different admission categories i.e. surgical, medical, trauma and neurological or neurosurgical patients.

Statistical significance was defined as a p value < .05. All data were analyzed using SPSS version 18.0 (SPSS, Chicago, IL).

Results

During the intervention period (2010-2011) 320 patients fulfilled the inclusion criteria and the control group (2008-2009) consisted of 432 patients. During the intervention period in total 143 patients were excluded for several reasons and in the control group 133 patients (Figure 1). Overall, 177 patients in the intervention group and 299 patients in the control group were evaluated. Patient and demographic characteristics are shown in Table 1. In the intervention group significantly more patients were admitted with sepsis compared with the control group. Twenty-two (12%) patients in the intervention and 46 (15%) patients in the control group were enrolled because of alcohol abuse or dementia.

Primary outcomes

The predicted chance to develop delirium in the intervention and control group was 75±19% and 73±22%, respectively. The actual delirium incidence was 65% in the intervention group, compared with 75% in the control group (Table 2).

Table 1 **Demographic and patients characteristics**

	Control group (N=299)	Intervention group (N=177)	Differences (p value)
Gender (M/%)	181 (61%)	115 (65%)	*.20*
Age	64±14	63±14	*.64*
APACHE-score	20±7	19±6	*.06*
Urgent admission (%)	261 (87%)	152 (86%)	*.52*
Sepsis (N/%)	64 (21%)	53 (30%)	*.02*
Admission specialism (N/%):			
- Surgical	75 (25%)	33 (19%)	*.99*
- Medical	143 (48%)	106 (60%)	
- Trauma	32 (11%)	18 (10%)	
- Neurology/neurosurgical	49 (16%)	20 (11%)	
PRE-DELIRIC score	73±22	75±19	*.50*
Other risk			
- Alcohol abuse	41 (14%)	20 (11%)	*.37*
- Dementia	5 (2%)	2 (1%)	

Data are presented as mean±standard deviation unless mentioned otherwise

The number of delirium free days was significantly higher in the intervention group (median 20 days [interquartile range 8-27] versus median 13 days [3-27]. Cox regression analysis was performed with sepsis as a covariate. Prophylactic treatment with haloperidol resulted in a relative 28-day mortality reduction of 20% (Exp(B) 0.80; 95%CI 0.66-0.98).

Figure 1 **Flowchart of inclusion of patients**

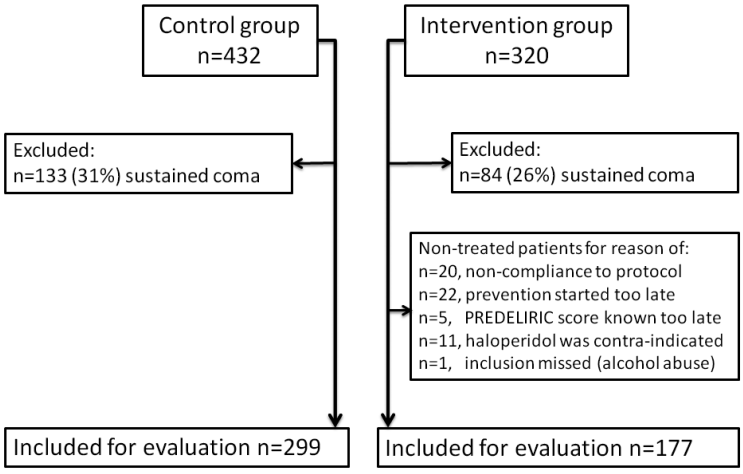
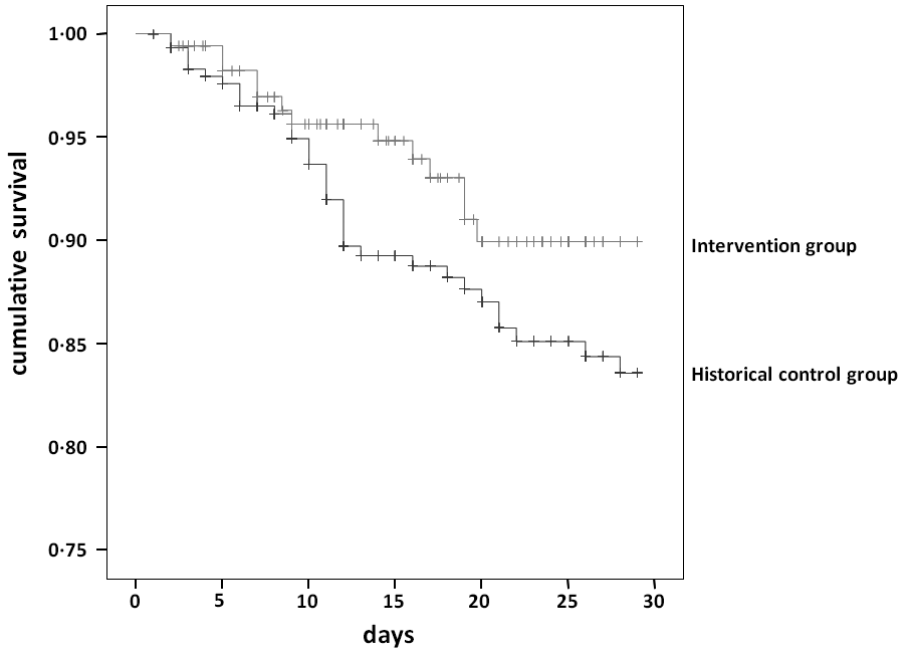


Figure 2 shows the 28-day Kaplan-Meijer survival curve of both groups. Although the APACHE-II score did not significantly differ between the two groups, when including this variable in the Cox-regression analysis together with sepsis the reduction is 16% (Exp(B) 0.84; 95%CI 0.69-1.02).

Figure 2 **Kaplan-Meijer survival plot of 28-day survival**



Secondary outcomes

No significant differences were found between groups in duration of mechanical ventilation, ICU- and hospital length of stay, and incidence of re-intubation. Patients who received prophylaxis were less likely to remove their tubes and catheters and were less likely to be re-admitted to the ICU (Table 2).

Risk groups and admission categories

To examine which patients benefit most from the prophylactic therapy with haloperidol the total group was equally divided in three groups based on their predicted risk. Patients with the highest risk appear to benefit most from the prophylactic treatment with haloperidol (Table 3).

Table 2 **Differences between control group and complete intervention group**

	Control group (N=299)	Intervention group (N=177)	Differences (p value)
Predicted delirium chance	*73±22*	*75±19*	
Observed delirium incidence	225 (75%)	115 (65%)	*.01*
Non-delirum:	74 (25%)	62 (35%)	*.38*
Delirium subtype:			
- Hyperactive	20 (7%)	6 (3%)	
- Hypoactive	81 (27%)	33 (19%)	
- Mixed	124 (41%)	76 (43%)	
Number of delirium free days without coma in 28 days	13 [3-27]	20 [8-27]	*.003*
Re-intubation (%)	25 (8%)	15 (9%)	*.51*
Duration mechanical ventilation in hrs.	118 [39-250]	90 [36-229]	*.24*
Unplanned removal tubes/lines (%)	58 (19%)	21 (12%)	*.02*
- Tube	8 (3%)	4 (2%)	
- Gastric tube	26 (9%)	14 (8%)	
- CVC/arterial line	24 (8%)	1 (<1%)	
- Other	0 (0%)	2 (1%)	
Re-admission	55 (18%)	20 (11%)	*.03*
LOS-ICU	7 [3-13]	6 [3-12]	*.65*
LOS-in hospital	21 [12-41]	20 [11-31]	*.16*
28-day mortality	36 (12%)	13 (7•3%)	*.03**

Data are presented as median, interquartile range [IQR], unless mentioned otherwise
** Cox regression analyses adjusted for sepsis and cohort (Exp(B) 0.80; 95%CI 0.66-0.98*

Results of prophylactic haloperidol treatment for the different admission categories are shown in Appendix A. The beneficial effects of prophylactic treatment were comparable between patient groups. Medical patients appeared to benefit most from prophylactic haloperidol treatment.

Non-treated patients during the implementation period

During the implementation period a total of 59 patients did not receive prophylaxis with haloperidol, mostly due to non-compliance to the new protocol. There were no demographic differences between the control group and the non-treated group (Appendix B, supplementary Table available online). The incidence of delirium, unplanned removal of tubes and re-admission rate was significantly higher and the number of delirium free days was significantly lower in the untreated group compared with the treated intervention group. In addition, the delirium incidence in the non-treated intervention group was also significantly higher compared with the treated intervention group (Appendix B, supplementary Table available online).

Haloperidol treatment

In 14 out of 177 (8%) patients adjustments in dosage were made because of possible side effects, with drowsiness as the most frequently mentioned reason (71%). Haloperidol was stopped in 12 (7%) patients because of prolonged QTc-time (n=9, all in patients treated with mild hypothermia), signs of Parkinsonism (n=1), renal failure (n=1) and in one patient malignant neuroleptic syndrome was suspected, but later not confirmed. Patients in whom the dosage of haloperidol was adjusted or stopped were allocated to the treated intervention group in the analyses.

Table 3 **Differences between control group and complete intervention group divided in 3 delirium risk groups**

Predicted chance <71%	**Control group (N=110)**	**Intervention group (N=69)**	**Differences (p value)**
Predicted chance	50±19	55±16	*.08*
Age	63±13	63±14	*.88*
APACHE-II score	17±5	16±5	*.12*
Sepsis (%)	11 (10%)	18 (26%)	*.005*
Observed delirium incidence	55(50%)	30 (44%)	*.27*
28 days delirium free without coma	26 [10-28]	26 [13-28]	*.17*
28-day mortality	13 (12%)	6 (9%)	*.34**
Re-intubation (%)	5 (5%)	6 (9%)	*.25*
Duration mechanical ventilation in hrs.	42 [14-150]	63 [15-168]	*.43*
Unplanned removal tubes/lines (%)	14 (13%)	7 (10%)	*.41*
- Tube	1 (1%)	1 (2%)	
- Gastric tube	2 (2%)	4 (6%)	
- CVC/arterial line	11(10%)	1 (2%)	
- Other	0 (0%)	1 (<1%)	
Re-admission	18 (16%)	4 (6%)	*.03*
LOS-ICU	3 [2-8]	4 [2-8]	*.32*
LOS-in hospital	17 [9-31]	16 [8-27]	*.48*
Predicted chance 71-89%	*(N=111)*	*(N=60)*	*Differences*
Predicted chance	81±5	80±5	*.66*
Age	64±14	61±15	*.14*
APACHE-II score	20±6	20±7	*.94*
Sepsis (%)	31 (28%)	24 (40%)	*.08*
Observed delirium incidence	94 (85%)	44 (73%)	*.06*
28 days delirium free without coma	11 [3-22]	20 [7-27]	*.02*
28-day mortality	13 (12%)	5 (8%)	*.93*
Re-intubation (%)	11 (11%)	6 (10%)	*.56*
Duration mechanical ventilation in hrs.	124 [55-278]	133 [50-281]	*.76*
Unplanned removal tubes/lines (%)	22 (20%)	8 (13%)	*.20*
- Tube	4 (4%)	2 (3%)	
- Gastric tube	12 (11%)	6 (10%)	
- CVC/arterial line	6 (5%)	0 (0%)	
Re-admission	27 (24%)	12 (20%)	*.33*
LOS-ICU	8 [3-15]	8 [4-17]	*.57*
LOS-in hospital	23 [13-43]	26 [16-41]	*.99*
Predicted chance>89%	*(N=78)*	*(N=48)*	*Differences*
Predicted chance	95±3	95±3	*.95*
Age	62±16	65±12	*.34*
APACHE-II score	24±8	21±6	*.05*
Sepsis (%)	22 (28%)	11(23%)	*.33*
Observed delirium incidence	76 (97%)	41 (85%)	*.06*
28 days delirium free without coma	4 [0-14]	13 [6-21]	*.002*
28-day mortality	10 (13%)	2 (4%)	*.07*[†]
Re-intubation (%)	9 (12%)	3 (6%)	*.25*
Duration mechanical ventilation in hrs.	185 [112-353]	94 [62-266]	*.02*
Unplanned removal tubes/lines (%)	22 (28%)	6 (13%)	*.04*
- Tube	3 (4%)	1 (2%)	
- Gastric tube	12 (15%)	3 (6%)	
- CVC/arterial line	7 (9%)	0 (0%)	
- Other	0 (0%)	2 (4%)	
Re-admission	10 (13%)	4 (8%)	*.32*
LOS-ICU	11 [7-18]	6 [4-15]	*.03*
LOS-in hospital	30 [14-56]	20 [15-31]	*.07*

Data are presented as median, interquartile range [IQR], unless mentioned otherwise

** Cox regression analysis with sepsis as covariate*

[†] Cox regression analysis with APACHE-II score as covariate

Discussion

We report that prophylactic treatment with haloperidol in ICU patients with a high risk for delirium results in a lower delirium incidence, associated with more delirium free days and a reduction in mortality compared to patients who did not receive prophylactic haloperidol. Importantly, only few side-effects of low dose haloperidol were reported of which none were severe. Our study may have important implications for daily practice in the ICU concerning prevention of delirium. Although prophylactic treatment with haloperidol was successfully used in elderly (7) and surgery patients (8), this is the first study in ICU patients that confirms these previous findings. In addition, our study shows that patients that received prophylactic haloperidol were less likely to remove their tubes or catheters or to be readmitted to the ICU, also illustrating the beneficial effects of prophylactic therapy with haloperidol.

While prophylactic therapy for delirium is sparsely studied in critically ill patients, more data is available concerning treatment of delirium. Haloperidol is recommended as first choice drug for delirium treatment (1;15;16). Several studies showed that use of other anti-psychotics than haloperidol (17-19) or use of other anti-psychotics in combination with haloperidol (20) does not further improve patient outcome, but could be even worsen it (21). These randomized trials demonstrated less severe or shorter duration of delirium, but were underpowered to detect an effect on length of stay or mortality (17-19). In an observational study a lower mortality rate in ICU patients was observed in ICU patients treated with haloperidol compared to those that were not treated (9). In addition, observational data also suggest that early treatment of delirium results in a lower mortality rate compared with delayed treatment (22). These data indicate that the effectiveness of early treatment, or possibly even better prophylaxis, may be superior compared to treatment of delirium. Importantly, prophylactic treatment of all ICU patients results in an unnecessary number of patients who are exposed to the side-effects of haloperidol. Therefore, there is a need for a delirium prediction model for ICU patients that identifies the patients with a high risk to develop delirium. In the present study we used our delirium prediction model with a high predictive value (10). Importantly, the higher the predicted risk, the more effective prophylaxis with haloperidol was.

Several limitations need to be addressed. Most importantly, we performed a case control study instead of a more powerful and controlled design such as a randomized controlled trial. Nevertheless, the fact that a better outcome was observed in patients that received prophylactic haloperidol also compared to case controls during the intervention period indicates that the results were not confounded by

a time-dependent bias. In addition, we chose relevant end-points known to be related to delirium. In view of the congruent effects of prophylactic treatment with haloperidol, this further supports the plausibility of our findings.

Second, potential side-effects of haloperidol were only obtained when spontaneously reported and mild extrapyramidal side-effects may have been missed, although a thorough physical examination of all patients is usual care in our ICU. Regarding QTc-time, this was measured daily and in 9 patients haloperidol was stopped for reason of prolonged QTc-time. This was probably due to the immediate start of haloperidol in the post-cardiopulmonary resuscitation phase after ICU admission combined with mild therapeutic hypothermia (23) in all 9 patients. Importantly, none of these patients developed ventricular arrhythmia as reported in some case reports (24-27). Furthermore, in several patients, haloperidol dose was adjusted for reasons of drowsiness or a possible sedative effect. Importantly, all these patients were delirious and these effects may also represent manifestations of delirium (1;14). The low incidence of side effects is in accordance with previous studies (7;8;28;29).

Third, the choice of the haloperidol dose likely influences the treatment effect. Our dosage was lower than the 5 mg/day that was used in surgery patients (8) which also resulted in a reduction of the delirium incidence. Similar to a study in elderly patients (7), we chose a lower dose in critically ill patients as they are also more likely to be vulnerable to the side-effects of haloperidol. In view of the few reported side-effects of haloperidol in our study and the still relatively high delirium incidence rate in ICU patients that received prophylactic treatment, a higher prophylactic dosage should be considered in future research.

In conclusion, prophylactic treatment with low dose haloperidol in critically ill patients with a high risk for delirium exerts several beneficial effects. With the encouraging results of the present study, we feel that a randomized prospective intervention study in ICU patients with a high risk for delirium using prophylactic haloperidol should be conducted. It should be considered, given the few side-effects of a low dose haloperidol, to also investigate the effect of a higher prophylactic dosage of haloperidol.

Acknowledgement

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Appendix A

Results of the prophylactic haloperidol treatment in the different admission categories

Surgical patients	**Control group (N=75)**	**Intervention group (N=33)**	**Differences (p value)**
Predicted chance (mean, SD)	62±25	62±24	*.68*
Observed delirium incidence	47 (63%)	18 (55%)	*.28*
28 days delirium free without coma	13 [3-28]	22 [10-28]	*.05*
28-day mortality	6 (8%)	1 (3%)	*.31*
Re-intubation (%)	7 (9%)	3 (9%)	*.64*
Duration mechanical ventilation in hrs.	57 [16-181]	20 [6-170]	*.21*
Unplanned removal tubes/lines (%)	12 (16%)	5 (15%)	*.58*
Re-admission	15 (20%)	7 (21%)	*.54*
LOS-ICU	8 [4-15]	3 [2-9]	*.55*
LOS-in hospital	23 [12-45]	20 [11-37]	*.92*
Medical patients	*(N=143)*	*(N=106)*	*Differences*
Predicted chance (mean, SD)	75±20	77±17	*.97*
Observed delirium incidence	116 (81%)	69 (65%)	*.003*
28 days delirium free without coma	11 [3-22]	20 [7-27]	*.04*
28-day mortality	20 (14%)	9 (9%)	*.13*
Re-intubation (%)	11 (11%)	9 (9%)	*.56*
Duration mechanical ventilation in hrs.	153 [72-330]	120 [63-260]	*.17*
Unplanned removal tubes/lines (%)	26 (18%)	9 (9%)	*.02*
Re-admission	30 (21%)	11 (10%)	*.02*
LOS-ICU	8 [3-15]	7 [4-14]	*.36*
LOS-in hospital	23 [13-43]	20 [11-34]	*.06*
Trauma patients	*(N=32)*	*(N=18)*	*Differences*
Predicted chance (mean, SD)	76±16	71±18	*.35*
Observed delirium incidence	22 (69%)	12 (67%)	*.56*
28 days delirium free without coma	14 [0-27]	20 [11-27]	*.59*
28-day mortality	1 (3%)	0 (0%)	*.64*
Re-intubation (%)	3 (9%)	2 (11%)	*.61*
Duration mechanical ventilation in hrs.	80 [17-284]	62 [19-261]	*.02*
Unplanned removal tubes/lines (%)	9 (28%)	5 (28%)	*.62*
Re-admission	1 (3%)	0 (0%)	*.64*
LOS-ICU	8 [3-14]	5 [4-16]	*.86*
LOS-in hospital	22 [14-40]	23 [15-28]	*.77*
Neurology/neurosurgical patients	*(N=49)*	*(N=20)*	*Differences*
Predicted chance (mean, SD)	82±18	87±16	*.26*
Observed delirium incidence	40 (82%)	16 (80%)	*.56*
28 days delirium free without coma	14 [4-26]	18 [15-27]	*.14*
28-day mortality	9 (19%)	3 (15%)	*.52*
Re-intubation (%)	7 (14%)	1 (5%)	*.28*
Duration mechanical ventilation in hrs.	112 [36-220]	71 [36-175]	*.43*
Unplanned removal tubes/lines (%)	11 (22%)	2 (10%)	*.22*
Re-admission	9 (18%)	2 (10%)	*.32*
LOS-ICU	6 [3-14]	6 [4-10]	*.89*
LOS-in hospital	20 [9-37]	19 [15-25]	*.70*

Data are presented as median, interquartile range [IQR], unless mentioned otherwise

Supplementary table online available

Appendix B

Non-treated patients in the intervention group compared with treated and control group

	Control group (N=299)	Intervention group non-treated (N=59)	Intervention group treated (N=177)
PRE-DELIRIC score (mean±sd)	73±22	77±17	75±19
Other risk			
- Alcohol abuse	41 (14%)	4 (7%)	20 (11%)
- Dementia	5 (2%)	0	2 (1%)
Age (mean±)	64±14	62±15	63±14
Urgent admission (%)	261 (87%)	52 (88%)	152 (86%)
APACHE-II score	20±7	20±6	19±6
Sepsis (%)	64 (21%) [b]	16 (28%)	53 (30%)
Gender (M/%)	181 (61%)	35 (59%)	115 (65%)
Admission specialism (N/%):			
- Surgical	75 (25%)	11 (19%)	33 (19%)
- Medical	143 (48%)	30 (51%)	106 (60%)
- Trauma	32 (11%)	5 (9%)	18 (10%)
- Neurology/neurosurgical	49 (16%)	13 (22%)	20 (11%)
Delirium incidence	225 (75%) [b]	53 (90%) [a-b]	115 (65%)
28 days delirium free without coma	13 [3-27] [b]	14 [1-22] [b]	20 [8-27]
28-day mortality	36 (12%) [b]	7 (12%)	13 (7%)
Re-intubation (%)	25 (8%)	8 (14%)	15 (9%)
Duration mechanical ventilation in hrs.	118 [39-250]	103 [54-251]	90 [36-229]
Unplanned removal tubes/lines (%)	58 (19%) [b]	13 (22%) [b]	21 (12%)
Re-admission	55 (18%) [b]	13 (22%) [b]	20 (11%)
LOS-ICU	7 [3-13]	7 [4-14]	6 [3-12]
LOS-in hospital	21 [12-41]	27 [13-48] [b]	20 [11-31]

Data are presented as median, interquartile range [IQR], unless mentioned otherwise
[a] statistically significantly different (p < .05) compared with control group
[b] statistically significantly different (p < .05) compared with treated intervention group

Supplementary table online available

PART FOUR

Role of Biomarkers related to Delirium in Intensive Care Patients

10

Endotoxemia-induced inflammation and the effect on the human brain

Mark van den Boogaard, Bart P. Ramakers, Nens van Alfen, Sieberen P. van der Werf, Wilhelmina F. Fick, Cornelia W. Hoedemaekers, Marcel M. Verbeek, Lisette Schoonhoven, Johannes G. van der Hoeven, Peter Pickkers

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Abstract

Introduction

Effects of systemic inflammation on cerebral function are not clear, as both inflammation-induced encephalopathy as well as stress-hormone mediated alertness have been described.

Methods

Experimental endotoxemia (2 ng/kg Escherichia coli lipopolysaccharide [LPS]) was induced in 15 subjects, whereas 10 served as controls. Cytokines (TNF-α, IL-6, IL1-RA and IL-10), cortisol, brain specific proteins (BSP), electroencephalography (EEG) and cognitive function tests (CFTs) were determined.

Results

Following LPS infusion, circulating pro- and anti-inflammatory cytokines, and cortisol increased ($p < .0001$). BSP changes stayed within the normal range, in which neuron specific enolase (NSE) and S100-β changed significantly. Except in one subject with a mild encephalopathic episode, without cognitive dysfunction, endotoxemia induced no clinically relevant EEG changes. Quantitative EEG analysis showed a higher state of alertness detected by changes in the central region, and peak frequency in the occipital region. Improved CFTs during endotoxemia was found to be due to a practice effect as CFTs improved to the same extent in the reference group. Cortisol significantly correlated with a higher state of alertness detected on the EEG. Increased IL-10 and the decreased NSE both correlated with improvement of working memory and with psychomotor speed capacity. No other significant correlations between cytokines, cortisol, EEG, CFT and BSP were found.

Conclusions

Short-term systemic inflammation does not provoke or explain the occurrence of septic encephalopathy, but primarily results in an inflammation-mediated increase in cortisol and alertness.

Introduction

With recorded prevalence rates of up to 70% (1), most patients with sepsis develop reversible brain dysfunction called sepsis-associated delirium or septic encephalopathy (2). In patients suffering from septic encephalopathy, electroencephalographic (EEG) abnormalities have been observed (2), although there are conflicting results concerning elevated levels of serum brain specific proteins (BSP) in septic patients (3;4). The mechanisms for brain dysfunction in septic patients are far from clear. Accumulating data suggest that circulating cytokines are associated with a neurotoxic effect in humans (1;2;5;6), either through a direct effect (7) or mediated via oxidative stress (8;9). In addition, genetic variation in the IL-1β-converting enzyme resulting in chronically higher levels of IL-1β is associated with memory and learning deficits (10). Moreover, there is evidence that increased levels of TNF-α and IL1-β further exacerbate ischemic and excitotoxic brain damage in humans (11;12).

On the other hand systemic inflammation induces a stress hormone response. This may lead to improvement of alertness, as throughout daytime temporal coupling between endogenous cortisol release and central alertness has been demonstrated in humans (13). Also, elevated cortisol concentrations and cortisol administration (13-19) were shown to improve cognitive functions (CF). Intravenous administration of Escherichia coli lipopolysaccharide (LPS) to young healthy volunteers induces an acute systemic inflammatory response mediated by high levels of cytokines, resulting in oxidative stress (9;20;21) and increased levels of cortisol (22). These effects are dose-dependent (23), and currently the administration of 2 or 4 ng/kg of LPS is mostly used in cases of experimental human endotoxemia. Human experimental endotoxemia can be used as a model to study the pathophysiological changes observed in septic patients, resulting in for example cardiac (24), vascular and endothelial dysfunction (21;25), coagulation abnormalities (26;27) and other subclinical end-organ dysfunction (28). However, up to now the effects of experimental human endotoxemia on brain function has not been adequately investigated. Although high-dose LPS infusion in mice results in encephalopathy (29), experiments in humans demonstrated conflicting results. Experimental endotoxemia resulted in no change (30), deterioration (31) or improvement and deterioration of different cognitive function tests (CFTs) (22). Endotoxemia-induced effects on EEG and BSP have not been investigated.

The aim of our present study was to investigate the effects of endotoxemia-induced inflammation on the brain. We addressed the question of whether LPS infusion induces changes in EEG, cortisol, BSPs, and CFs. Furthermore we wanted to examine if there is a correlation between the LPS-induced increased level of cytokines, cortisol, changes in EEG signals, BSPs and various CFs.

Material and methods

Study design of human endotoxemia experiments

This study is registered at the Clinical Trial Register under the number NCT00513110. After approval of our ethics committee, 15 healthy male volunteers gave written informed consent to participate in the LPS study. Screening before the experiment revealed no abnormalities in medical history or physical examination. Routine laboratory tests and electrocardiogram (ECG) were normal and the volunteers had no reported brain dysfunction or psychiatric disorders. Ten healthy male volunteers were recruited for only cognitive measurements after they gave informed written consent.

During the experiment all 15 volunteers were monitored for heart rate (ECG), blood pressure (intra-arterially), body temperature (infrared tympanic thermometer; Sherwood Medical, 's-Hertogenbosch, the Netherlands) and EEG activity (Nicolet One system, Viasys Healthcare, Houten, The Netherlands), from about two hours before the administration of LPS and continued until the end of the experiment (about eight hours after the LPS administration). A cannula was inserted in a deep forearm vein for prehydration (1.5 L of 2.5% glucose/0.45 saline solution in the hour before LPS administration). During the first six hours after the LPS administration all subjects received 150 mL/h, and after that period until the end of the experiment 75 mL/h of 2.5% glucose/0.45 saline solution to ensure an optimal hydration status (32).

In one minute *E. coli* LPS 2 ng/kg was injected at t = 0 hours. The course of symptoms (headache, nausea, shivering, muscle pain and back pain) were scored on a six-point Likert scale; 0 = no symptoms, 5 = very severe symptoms, resulting in a total score of 0 to 25.

Laboratory tests (cytokines, cortisol and brain specific proteins)

Analysis of cytokines and cortisol

All blood was allowed to clot and after centrifugation serum was stored at -80°C until analysis.

To determine the time course and peak values per individual, serial blood samples were taken. Cytokines concentrations of TNF-α, IL-6, IL-1-receptor antagonist, and IL-10 were measured in samples taken at baseline (t = 0) and at one, two, four and eight hours after LPS administration and batchwise analysed using Luminex assay. Cortisol levels were determined with luminometric immunoassay on a random access analyzer (Architect® i System, Abbott, Illinois, USA) at baseline (t = 0) and at 2-4-8 hours after LPS administration.

Analysis of brain specific proteins: S100-β, NSE, and GFAP

Proteins S100 calcium binding protein-β (S100-β) and neurospecific enolase (NSE) were analyzed using a commercially available monoclonal two-site luminometric assay (Sangtec Medical, Dietzenbach, Germany) according to the manufacturer's instructions using a Liaison automated analyzer (Byk Sangtec, Dietzenbach, Germany). The lower detection limit for S100-β is 0.02 μg/L. The upper reference range (95%) of S100-β serum concentrations in healthy subjects is 0.12 μg/L. The lower detection limit for NSE is 0.04 μg/L, and the upper reference range (95%) of NSE in serum from healthy subjects is 12.5 μg/L. The glial fibrillary acidic protein (GFAP) assay is a two-site luminometric assay. The serum sample is pipetted into coated wells of a microtitre strip containing the tracer antibody labelled with an isoluminol derivative. After incubation, the strips are washed and the chemiluminescent signal is measured in a luminometer. All steps of the assay are performed at room temperature. The lower detection limit for GFAP is 0.02 μg/L, and the upper limit (95%) of GFAP in serum in 75 healthy subjects was 0.49 μg/L.

Electroencephalography

Subjects were monitored continuously with EEG, using a standard 21-lead recording with surface Ag/AgCl cup electrodes that were attached with Elefix EEG paste (Nihon Koden Inc., Foothill Ranch, California, USA) and placed according to the international 10-20 system. Recordings were made from electrode positions Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, A1, A2, O1, and O2. Additional electrodes were placed for the recording of ocular movements and the ECG. Electrode impedance was kept below 5 KOhm, and the signals were filtered with a 1 Hz (high-pass) and 70 Hz (low-pass) filter. EEG signals were digitally sampled with a frequency of 256 Hz and stored on a computer hard disk. The full-length recordings were analyzed visually by an experienced clinical neurophysiologist (NvA) blinded to the LPS protocol. Raw EEGs were scored using a five category classification system for septic encephalopathies (33). At least once per hour a one-minute artefact-free raw EEG sample (10-second epoch) of the subject lying awake with his eyes closed was selected for further quantitative analysis. In each subject, the power spectrum of samples was calculated for the standard frequency bands (delta <4 Hz; theta 4 to <8 Hz; alpha 8 to <13 Hz, beta >13Hz) using Fourier transformation. The peak frequency in the occipital regions (P3 to O1 and P4 to O2 bipolar montages) was assessed for each time point. To detect changes in central alertness alpha and beta activity changes in the relative band power and absolute band power of the occipital and central electrodes (P4O2, P3O1 and F4C4, F3C3, respectively) were used, and also changes in peak frequency in the occipital region (13). Changes in activity were expressed as percentage of change of the individual baseline level of activity before the LPS administration.

Cognitive function tests

The anxiety level of each individual was measured at baseline after arrival at our research unit, with the Dutch State-Trait Anxiety Inventory (STAI) scale (34). Higher scores (range 0 to 80) indicate higher levels of psychological distress. The time the participants required to finish the Grooved Pegboard test with the dominant hand served as an indication of fine motor control (35). Working memory was assessed with the digit span forward and backward subtests of the Dutch translations of the Wechsler Adult Intelligence Scale (WAIS) III (36). The total number of correct responses on the two-second stimulus interval condition of the Paced Auditory Serial Addition Test (PASAT) served as a measure for divided attention under time pressure (37). The total number of correct responses on the Digit Symbol Test (SDT) of the WAIS III was chosen as an indication of psychomotor speed capacity as well as the information processing ability (36). Reading speed, colour naming speed and distractibility were measured with the Stroop colour-word naming test (38) (Pearson Assessment and Information B.V., Amsterdam, The Netherlands). To measure a possible practice effect as a result of test-retesting of the CFTs, the same CFTs under the same conditions and time intervals were performed in a reference group of 10 healthy male volunteers that did not receive LPS.

Data analysis and statistics

All data were analyzed using SPSS version 16.01 (SPSS, Chicago, Illinois, USA). Results are expressed by means ± standard error of the mean or median (interquartile range (IQR)) depending on their distribution. LPS-induced effects were tested for significance with Friedman's analysis of variance (non-parametric test). To detect practice effect we compared the experimental group and the reference group with the repeated measurement-analysis of variance. Correlation analysis was performed with the Spearman's correlation coefficient. Because of the exploratory nature of this study, a correction for multiple testing was not included. Statistical significance was defined as a p value less than .05.

Results

Baseline characteristics

Baseline characteristics of the 15 healthy male volunteers are shown in Table 1. All participants had a mean age of 23 ± 2 years, and had a high (college or university) educational level.

Table 1 Baseline demographic characteristics of the study group

Characteristic (n = 15)	
Age (years)	23 ± 2
Height (cm)	186 ± 7
Weight (kg)	77.1 ± 9.0
Body mass index (kg/m^2)	22.3 ± 2.0
Systolic blood pressure (mmHg)	130 ± 6
Diastolic blood pressure (mmHg)	65 ± 9
Heart rate (bpm)	61 ± 8
Temperature (ºC)	35.7 ± 0.3
Symptom score (median)	0 (IQR 0-1)

All values are means ± standard deviation unless other reported

LPS-induced changes in clinical and inflammatory parameters and cortisol levels

LPS administration induced the expected transient flu-like symptoms. Body temperature increased by 1.4 ± 0.1ºC (p < .0001) and heart rate by 27 ± 2 bpm (p < .0001). Cumulative symptom scores increased from a median score of 0 (IQR 0 to 1) to 4 (IQR 2 to 7) at 70 minutes after LPS administration, after which there was a decrease to a median of 2 (IQR 1 to 5) and 1 (IQR 0 to 2) at two and four hours, respectively (p < 0.0001). Relevant to the present study, LPS administration induced an increase in headache score from 0 score to a maximum of 2 (IQR 1 to 3) at 90 minutes after endotoxin administration (p < .0001).

All plasma cytokine concentrations increased significantly (all p < .0001) after the administration of LPS (Figure 1). Cortisol levels increased significantly from 0.31 ± 0.07 to 0.60 ± 0.07 µmol/l (p < .0001) two hours after LPS administration and dropped to baseline levels eight hours after LPS administration (Figure 1).

LPS-induced changes in brain specific proteins

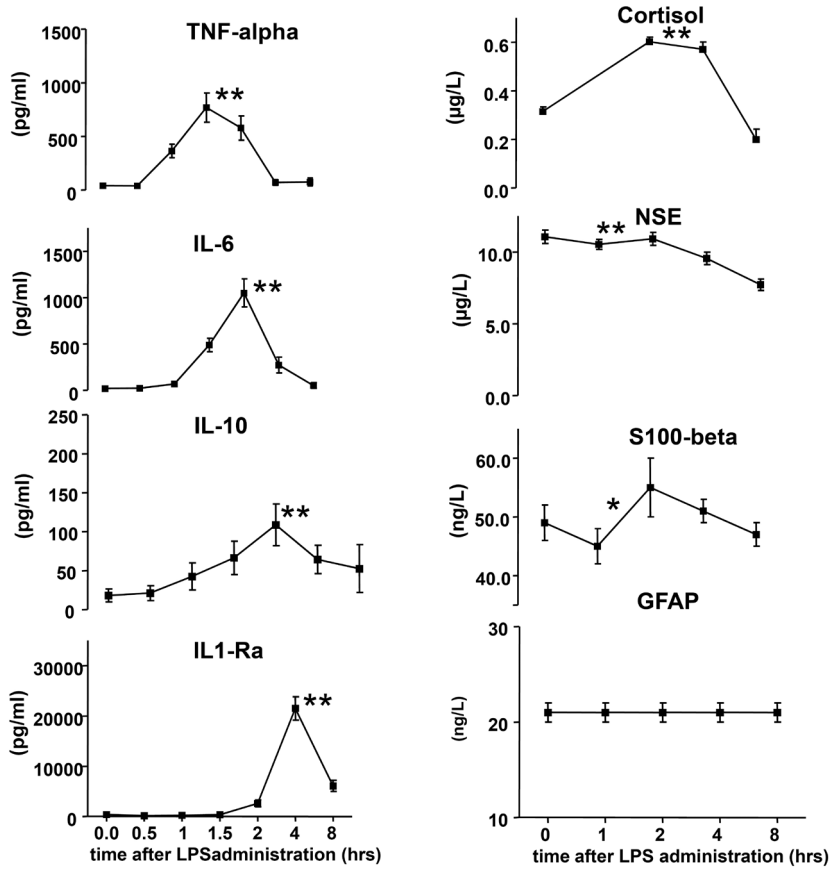
As illustrated in Figure 1, NSE levels showed a small, but statistically significant decrease from 11.1 ± 0.47 to 7.7 ± 0.39 µg/L after the administration of LPS ($p < .0001$). S100-β showed a significant biphasic change (from 0.049 ± 0.002 up to 0.055 ± 0.004 and down to 0.047 ± 0.002 µg/L, $p = .04$), whereas GFAP levels did not change significantly ($p = .41$).

LPS-induced changes in EEG

Visual analysis

For each subject, at least eight hours of raw EEG were available for visual analysis. All EEGs before LPS infusion were within the normal range. One hour after LPS infusion mild transient encephalopathic EEG changes in the theta range were present in one subject for 15 minutes, without associated cognitive impairment. Of note, this subject had a very low cytokine response during endotoxemia (TNF-α level of 169 pg/ml compared with the group mean of 814 ± 133 pg/ml, and IL-6 level of 508 pg/ml compared with the group mean of 1,111 ± 142 pg/ml) and an average cortisol response (0.29 to 0.67 µmol/l). The EEGs from the other 14 subjects remained within the normal range after LPS infusion, and no focal or epileptiform abnormalities were found.

Figure 1 **LPS-induced changes in cytokine plasma concentrations, cortisol and brain specific proteins.**



*Time -0- reflects baseline concentrations. Administration of lipopolysaccharide (LPS) resulted in a marked increase in TNF-α, IL-6, IL-10, IL-1Ra and cortisol concentrations. All changes in cytokine and the cortisol concentrations were significant (p < .001). Concentrations of neuron specific enolase (NSE) decreased after administration of LPS (p < .001) and S100-β showed a significant biphasic change (p = 0.038). All data are expressed as mean ± standard error of the mean (n = 15). GFAP, glial fibrillary acidic protein; S100β, S100 Calcium Binding Protein B. * p < .05. ** p < .001.*

Table 2 **Neuropsychological test outcomes (mean ± SD) at 0 (baseline), 2 and 8 hours after LPS administration**

	LPS group (n = 15)				Reference group (n = 10)				p-value (between group)
Age	22.8 ± 2.2				25.5 ± 2.5				*.87**
(Dutch) STAI total	32.7 ± 1.5				29.1 ± 3.7				*.13**
Neuropsychological test	***t = 0***	***t = 2***	***t = 8***	**p-value** (within group)	***t = 0***	***t = 2***	***t = 8***	***P value*** *(within group)*	
Stroop A (in seconds) [1]	39 ± 2	35 ± 2	35 ± 2	*.0001*	37 ± 5	34 ± 4	34 ± 4	*.001*	*.49*
Stroop B (in seconds) [1]	51 ± 3	45 ± 3	43 ± 2	*.0001*	48 ± 7	44 ± 7	43 ± 7	*.001*	*.45*
Stroop C (in seconds) [1]	75 ± 6	65 ± 4	64 ± 4	*.003*	67 ± 10	62 ± 12	61 ± 11	*.004*	*.23*
Pasat [2]	49 ± 2	50 ± 2	56 ± 2	*.001*	50 ± 7	54 ± 4	54 ± 5	*.031*	*.07*
Digits forward [2]	11 ± 1	12 ± 1	11 ± 1	*.115*	10 ± 2	11 ± 1	11 ± 2	*.235*	*.81*
Digits backward [2]	8 ± 1	9 ± 1	9 ± 1	*.30*	9 ± 2	9 ± 1	9 ± 2	*.454*	*.65*
Digits total [2]	19 ± 1	20 ± 1	20 ± 1	*.066*	19 ± 4	20 ± 3	21 ± 4	*.203*	*.63*
Pegboard [1]	64 ± 2	59 ± 2	61 ± 2	*.037*	58 ± 5	56 ± 6	56 ± 7	*.362*	*.35*
Symbol substitution task[2]	87 ± 3	99 ± 4	101 ± 3	*.0001*	98 ± 14	108 ± 17	112 ± 19	*.0001*	*.53*

*All values are means ± SD unless other reported. * Unpaired T-test.*
[1] Decrease indicates an improvement of the test. [2] Increase indicates an improvement of the test.
Reading speed was measured by Stroop A-B-C word naming test.
Attention under time pressure was measured by the paced auditory serial addition test (PASAT).
Working memory was tested in numbers with the Digits forward and backward test .
The fine motor control was tested with the Grooved Pegboard test.
Psychomotor speed capacity was measured by the symbol substitution task.
LPS, lipopolysaccharide; SD, standard deviation; STAI, Dutch State-Trait Anxiety Inventory scale.

Quantitative analysis

LPS induced a significant increase of the peak frequency and absolute band power of alpha and beta activity in the occipital region, P4O2 and P3O1 (all $p < .0001$). The absolute power of the alpha activity in the central region, F4C4 and F3C3, increased significantly (both $p < .0001$). The relative band power of the beta activity in P4O2 increased significantly ($p = .017$), indicating a higher state of alertness. No other relevant EEG changes were found (Figure 2).

LPS-induced changes in cognitive function

Baseline STAI in the LPS group was 32.7 ± 1.5, indicating a low level of anxiety that did not differ from the reference group 29.1 ± 3.7 ($p = 0.13$). During endotoxemia all measured CFs significantly improved. These improvements were not significantly different from those observed in the reference group who did not receive LPS (Table 2), indicating that the improvement of the CFT in the LPS group was due to a practice effect.

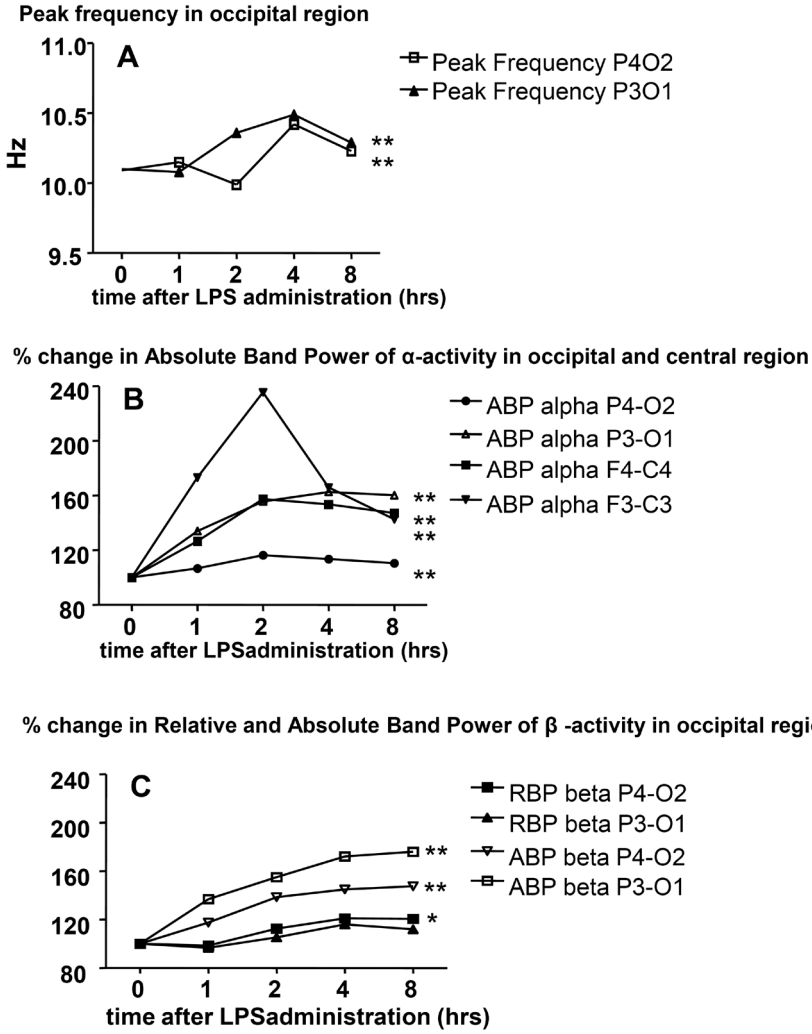
Correlation analyses

Cytokines, cortisol, BSP, EEG, and CF

To analyse the effects between the measured cytokine levels, cortisol, BSP levels, EEG parameters and cognitive performances, data were correlated.

In the LPS group the elevated levels of the anti-inflammatory cytokine IL-10 significantly correlated with the improvement of the working memory (r = 0.71, p = .003) and the psychomotor speed capacity (r = 0.71, p = .003). The increased cortisol levels significantly correlated with the increased peak frequency in the occipital electrodes P4O2 (r = 0.61, p = .016) and P3O1 (r = 0.69, p = .005). In the LPS group, the decreased level of NSE significantly correlated with the improvement of the working memory and psychomotor speed capacity (r = -0.53, p = .048 and r = -0.67, p = .006, respectively). The increased alpha activity in F3C3 central region correlated significantly with the improvement of the working memory (r = 0.66, p = .007). No other correlations between cytokines, cortisol, BSP, EEG and CF were found.

Figure 2 **Increase of the EEG occipital peak frequencies, relative alpha band power and absolute alpha and beta band power two to three hours after LPS infusion.**



*Data of peak frequency are absolute numbers, data of absolute and relative band power are expressed as percentage changes. Time -0- reflects baseline measurements. (standard error of the means were omitted for reasons of clarity). * p < .05. ** p < .001. (a) Peak frequency in occipital region. Friedman analysis of variance revealed changes in P4O2 and P3O1 (both p < .001). (b) Percentage change compared to baseline in absolute band power (ABP) of alpha activity in occipital and central region. Friedman analysis of variance revealed changes for alpha activity in P4O, P3O1 and F4C4, F3C3 all p < .001. (c) Percentage change compared with baseline in absolute band power (ABP) and relative band power (RBP) of beta activity in occipital region. Friedman analysis of variance revealed changes of RBP for beta activity in P4O2 (p = .017), P3O1 (p = .575) and ABP for beta activity in P4O and P3O1 (both p < .001).*

Discussion

The main result of the present study is that, despite very high cytokine concentrations during experimental endotoxemia, no indications were found that acute systemic inflammation results in increased levels of BSPs and deterioration of CFs in humans in vivo. In addition, a group level quantitative EEG analysis showed a higher state of alertness that correlated with cortisol concentrations. Nevertheless, the concomitant improvement in CFTs turned out to represent a practice effect as a similar improvement was observed in subjects who did not receive LPS. Although the increased alpha activity in the central region of the brain correlated with the improvement of working memory in the LPS group, it appears conceivable that this correlation may also be present in the control group during the repeated CFTs, but this finding needs to be confirmed. Interestingly, the one subject with a transient mild encephalopathic episode on EEG, that is category 2 following the score used by Young and colleagues (33), showed that this was not associated with objective cognitive dysfunction. In addition, this subject had one of the lowest LPS-induced proinflammatory cytokine responses of the whole group, arguing against a cytokine-mediated effect.

Although experimental endotoxemia in young humans without any co-morbidity mimics the pathophysiological changes in septic patients in many ways, important differences also exist. For example, TNF-α concentrations found during experimental endotoxemia are much higher than in septic patients, whereas other cytokines are released to a lesser extent and some inflammatory mediators found in septic patients are not induced during experimental endotoxemia (39). It appears likely that the relatively mild insult and short duration of elevated cytokine levels during experimental endotoxemia does account for the increase in cortisol concentration and observed stimulating effects on the brain, but may not reflect the neurotoxic effects of inflammatory mediators present in septic patients. In addition, age and the pre-existing neurological situation is likely to be important. Healthy elderly people show a more pronounced inflammatory response during experimental endotoxemia (40) and pre-existing micro-glial inflammation primes the brain for development of cognitive impairment in non-infectious and infectious central nervous system dysfunction (41). Therefore, although our study shows that a short duration of very high cytokine levels is not associated with brain dysfunction it does not exclude the possible effects of cytokines on neurons in older ICU patients with co-morbidities.

Cortisol secretion is related to electroencephalographic alertness (13). We showed a significant correlation between the elevated levels of cortisol and the change in occipital peak frequency. It is likely that this higher state of alertness was due to the

LPS-induced inflammation with feelings of sickness resulting in a stress hormone-driven 'flight-fight' response (42), which is also associated with increased cortisol. This appears to be a short-lived effect, because chronically elevated levels of glucocorticoids result in a deterioration of CF (43). As a result of this, it is possible that in the septic patient the stimulating effect of stress hormones on the brain is overshadowed by the neurotoxic effect of persistently elevated level of cytokines and other mediators. In septic patients, levels of some proinflammatory cytokines are not as high as in the LPS model, but the duration of the elevated cytokine level is much longer (44). If these cytokines play a role in the sepsis-associated encephalopathy, it is apparently not the absolute peak concentration of the proinflammatory cytokine that is of importance. Presumably, sustained elevated levels of cytokines are more important in the development of organ failure and brain dysfunction in sepsis. In accordance, chronic small increases in proinflammatory cytokine levels due to polymorphisms were found to be associated with decreased brain function (10). Naturally, other not yet identified mediators of inflammation that may be increased in septic patients but not during experimental endotoxemia may also account for brain dysfunction observed in septic patients.

In previous studies with much lower doses of LPS (0.2 to 0.8 ng/kg), with little systemic inflammatory response, conflicting effects on CFs were reported (22;30;31). Compared with experiments with 0.2 ng/kg, improvement of working memory was shown in a study with 10 healthy volunteers with a dose of 0.8 ng/kg LPS (22). In these studies, cortisol level and cytokines increased slightly, compared with our results (22;30;31), which is associated with dysfunction of other organs (24;28;45). Furthermore, a potential problem in the studies with low doses of LPS was that no correction for practice effect was performed while practice effects during CFT are common, especially in situations with short test-retest intervals. Our study demonstrates that the observed improvement in CFs after LPS infusion in all domains was due to a practice effect. Without the use of a control group and the measurement of practice effect results are bound to be misinterpreted. Our results suggest that a short-term inflammation does not influence practice effect or lead to a significant deterioration or improvement of CFs.

The observed relations between EEG changes and inflammatory markers indicate a higher state of inflammation-induced alertness. Higher dosages of LPS result in higher levels of cytokines (23) and more elevated levels of cortisol result in a higher state of alertness (13). The higher state of alertness during endotoxemia is possibly a so-called fight and flight response, rather than being due to the increased cytokine concentrations.

Although it is tempting to speculate, due to the observational nature of the present study we cannot conclude whether or not the anti-inflammatory innate

immune response, measured by IL-10, exerts a protective effect on the brain, and this correlation needs further study. In addition, the pathophysiological mechanism by which systemic inflammation results in the observed decrease of NSE is not clear. Increased levels of NSE are associated with deterioration of CF after cardiac surgery (46). Also, increased NSE levels are associated with brain injury in septic patients, but an association between NSE and CFs in septic patients has not been examined.

Conclusions

Administration of LPS to humans results in systemic inflammation with high levels of cytokines and increased cortisol levels. In young healthy volunteers this can sporadically lead to a transient mild deterioration of brain function without clinical correlation. Overall, LPS infusion results in a higher state of alertness determined on the EEG, while the practice effects in CFTs are not significantly influenced. Short-term systemic inflammation does not provoke or explain the occurrence of a septic encephalopathy.

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11

Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients

Mark van den Boogaard, Matthijs Kox, Kieran L. Quinn, Theo van Achterberg, Johannes G. van der Hoeven, Lisette Schoonhoven, Peter Pickkers

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ABSTRACT

Introduction

Delirium occurs frequently in critically ill patients and is associated with disease severity and infection. Although several pathways for delirium have been described, biomarkers associated with delirium in intensive care unit (ICU) patients is not well studied. We examined plasma biomarkers in delirious and nondelirious patients and the role of these biomarkers on long-term cognitive function.

Methods

In an exploratory observational study, we included 100 ICU patients with or without delirium and with ("inflamed") and without ("noninflamed") infection/systemic inflammatory response syndrome (SIRS). Delirium was diagnosed by using the confusion-assessment method-ICU (CAM-ICU). Within 24 hours after the onset of delirium, blood was obtained for biomarker analysis. No differences in patient characteristics were found between delirious and nondelirious patients. To determine associations between biomarkers and delirium, univariate and multivariate logistic regression analyses were performed. Eighteen months after ICU discharge, a cognitive-failure questionnaire was distributed to the ICU survivors.

Results

In total, 50 delirious and 50 nondelirious patients were included. We found that IL-8, MCP-1, procalcitonin (PCT), cortisol, and S100-β were significantly associated with delirium in inflamed patients (n = 46). In the noninflamed group of patients (n = 54), IL-8, IL-1ra, IL-10 ratio Aβ1-42/40, and ratio AβN-42/40 were significantly associated with delirium. In multivariate regression analysis, IL-8 was independently associated (odds ratio, 9.0; 95% confidence interval (CI), 1.8 to 44.0) with delirium in inflamed patients and IL-10 (OR 2.6; 95% CI 1.1 to 5.9), and Aβ1-42/40 (OR, 0.03; 95% CI, 0.002 to 0.50) with delirium in noninflamed patients. Furthermore, levels of several amyloid-β forms, but not human Tau or S100-β, were significantly correlated with self-reported cognitive impairment 18 months after ICU discharge, whereas inflammatory markers were not correlated to impaired long-term cognitive function.

Conclusions

In inflamed patients, the proinflammatory cytokine IL-8 was associated with delirium, whereas in noninflamed patients, antiinflammatory cytokine IL-10 and Aβ1-42/40 were associated with delirium. This suggests that the underlying mechanism governing the development of delirium in inflamed patients differs from that in noninflamed patients. Finally, elevated levels of amyloid-β correlated with long-term subjective cognitive-impairment delirium may represent the first sign of a (subclinical) dementia process. Future studies must confirm these results.

Introduction

Delirium is a serious and frequently occurring disorder in critically ill patients associated with both physical and cognitive impaired outcome (1-4). Because the pathogenesis of delirium is probably multifactorial, biomarker analysis may provide valuable information regarding the underlying mechanisms (5-7).

Several previous investigations in non-ICU patients established an association between inflammation and delirium, as correlations between proinflammatory cytokine levels and delirium have been found (6;8-10). Furthermore, in elderly delirious patients with hip fractures, increased concentrations of IL-6, IL-8 and cortisol were correlated with elevated levels of the brain specific protein (BSP) S100-β (a marker for astrocyte damage) (11). Interestingly, sepsis is also associated with elevated levels of BSP (12;13). Furthermore, it has been hypothesized that serious illness such as sepsis, as well as the use of sedatives and analgesic, could result in apoptosis and long-term cognitive impairment (14). mice, tumor-necrosis factor (TNF)-α is a mediator of apoptotic cellular death in the brain (15), and may therefore be causally associated with the development of delirium in patients with severe inflammation.

In the long-term delirium is associated with an over 12-fold increased risk for developing dementia (16), resulting in permanent impairment of cognitive function that is associated with altered levels of amyloid-β (17;18). The association between biomarkers in delirious patients and long-term cognitive function are unknown.

With regard to its multifactorial nature, it is likely that the underlying mechanisms of delirium may differ between inflamed and noninflamed patients. In the present study, we explored which biomarkers were associated with delirium in inflamed patients and which were associated with delirium in noninflamed patients, thereby using these biomarkers to explore whether different underlying mechanisms are involved. We included biomarkers that are directly linked to delirium, as determined in previous studies, and biomarkers that are linked with the onset of delirium. Apart from well-established pro- and antiinflammatory cytokines, we determined, for example, procalcitonin (19), macrophage migration inhibitory factor (20) and human neutrophil peptide-1 (21) that play a role in inflammation, directly associated to delirium (22). Finally, we searched for correlations between mediators that were related to delirium and brain-specific proteins and cognitive functions 18 months after ICU discharge to establish whether the different pathways exert different long-term cognitive effects.

Material and methods

Patients and definitions

A convenience sample was taken of all medical and surgical patients older than 18 years admitted to our Intensive Care Department (tertiary referral hospital in Nijmegen, the Netherlands) between February and July 2008. These patients were screened for delirium using the confusion assessment method-ICU (CAM-ICU) (23;24). Patients were excluded when delirium screening during patients' complete ICU stay could not be performed (for example, because of persistent coma). Patients who were admitted to the ICU for trauma, postcardiac arrest, or neurologic reasons were also excluded. Finally, patients were excluded when they had a history of serious cognitive impairment, defined as reported in their medical history, or had from any form of dementia, delirium, or obvious signs of cognitive impairment reported by their relatives. If doubt existed concerning preexistent cognitive function, patients were not included in this study.

In delirious patients, blood was drawn within 24 hours after the onset of delirium. For the nondelirious group, because no point in time exists to relate to, we draw blood after a similar ICU length of stay compared with that of the group of delirious patients. A total of 5 ml blood was drawn for all measurements.

In delirious patients, blood was drawn within 24 hours after the onset of delirium. For the nondelirious group, there is no point in time to relate to. Therefore we draw blood after a similar ICU length of stay compared to the group of delirious patients. A total of 5 ml blood was drawn for all measurements. Delirium and nondelirium patients were furthermore divided into inflamed and noninflamed patients. This distinction was made because inflamed patients are suspected to have high levels of inflammatory mediators, and from a group of noninflamed patients, it is expected that they have low levels of inflammatory mediators. Inflamed was defined as a positive culture, regardless the origin from which specimens were taken, for which the patient was treated with antibiotics. Although systemic inflammatory response syndrome (SIRS) criteria lack specificity, the study was designed to differentiate between inflamed patients and noninflamed patients, and therefore, we used the presence of more than two SIRS criteria as a marker of inflammation (25). Absence of inflammation was defined as the absence of proven or suspected infection and the presence of no more than of one SIRS criterion.

The regional Medical Ethics Committee of Arnhem-Nijmegen approved the study and waived the need for informed consent because a single blood withdrawal is not considered a burden for the patient, and the results of this study did not influence the standard care for that patient. The study was registered in the Clinical Trial Register (NCT00604773).

Procedures

Demographic variables as well as illness related characteristics were collected. The validated CAM-ICU method was used to detect whether patients were delirious. All patients were screened at least 3 times per day by using the CAM-ICU with a high interrater reliability of 0.90 (95%CI 0.82-0.98) Cohen's kappa by well trained ICU-nurses (26). Patients were diagnosed with delirium when they had at least one positive CAM-ICU screening. Patients without any positive CAM-ICU screening during the complete ICU stay were classified as nondelirious. In case of doubt regarding the delirium diagnosis, patients were not included in this study.

Blood for the determination of biomarkers was drawn between 6 and 10 a.m. and within 24 hours of the first positive CAM-ICU screening from an indwelling arterial line. Blood was centrifuged at 2,000 g for 15 minutes, and plasma was stored at -80 °C until analysis. Proinflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-17, IL-18 and macrophage migration inhibitory factor (MIF), antiinflammatory cytokines (IL-1RA and IL-10), and the chemotactic cytokine MCP-1 were determined using a simultaneous Luminex assay (Milliplex, Millipore, Billerica, MA, USA). Plasma defensin (human neutrophil peptide-1 (HNP-1) was measured using mouse anti-human HNP-1-3 monoclonal antibody (HyCult Biotechnology, Uden, The Netherlands) and the wells were then incubated with rabbit anti-human HNP-1-3 polyclonal antibody (Host Defence Research Centre, Toronto, Canada), followed by incubation with peroxidase-conjugated goat-anti-rabbit IgG (Jackson ImmunoResearch). C-reactive protein (CRP) concentrations were measured using immunological detection (turbidimetric method, Aeroset, Abbott Laboratories, Abbott Park, IL, USA) and procalcitonin (PCT) levels were determined using an immunometric assay with time-resolved amplified cryptate emission technology (PCT sensitive Kryptor kit; Brahms, Germany). The stress hormone cortisol was measured with luminometric immunoassay on a random access analyzer (Architect® i System, Abbott, Il, USA).

The brain specific proteins full length amyloidβ1-42 and 1-40 (Aβ1-42 and Aβ1-40) and truncated Aβ-42 and -40 (AβN-42 and AβN-40) were determined in plasma using a simultaneous Luminex assay (INNO-BIA plasma Aβ forms, Innogenetics, Ghent, Belgium) which has been shown to be a reliable assay with a low variability (27). Plasma levels of S100 calcium binding protein-β (S100-β) and total human Tau were analyzed using two commercially available ELISA kits (Cosmo Bio Co. Ltd; Tokyo, Japan and Cusabio biotech Co Ltd, Donghu; China, respectively). All biomarkers were determined according to the manufacturer's instructions.

Subjective long-term cognitive functioning

All included patients received the validated Dutch translation (28) of the cognitive

failure questionnaire (CFQ) 18 months (median) after discharge from the ICU (29). The self reported CFQ measures four dimensions of cognition: memory, distractibility, social blunders, and names (30). Each question was scored on a 5-point Likert scale. The total score on the CFQ ranges from 0-100, a higher score indicates more severe cognitive dysfunctioning. The subjective CFQ shows good correlation with more quantitative mental health tests (29). An extensive description concerning the use of the CFQ in critically ill patients was recently published (31).

Statistical analysis

Differences in baseline characteristics between delirious and nondelirious patients were tested by using $\chi 2$ tests and the Mann-Whitney *U* or Student t tests, depending on its measure and distribution. Biomarkers and CFQ data were successfully log transformed to obtain normally distributed data. To determine the association between biomarkers and delirium in the inflamed and the noninflamed group of patients, univariate logistic regression analysis was performed. To examine the associations between the biomarkers and delirium, a multivariate logistic regression analysis method backward conditional was performed, including biomarkers with the 10 best-associated biomarkers in the univariate analysis. Correlations between biomarkers and CFQ outcomes, measured 18 months after ICU discharge, were determined by using Pearson's correlation coefficients.

Because of the exploratory nature of this study, no correction for multiple testing was performed to increase sensitivity. Statistical significance was defined as a p value < 0.05.

All data were analyzed by using SPSS version 16.01 (SPSS, Chicago, IL, USA).

Results

In total, 105 patients were screened for this study, of which 5 patients were excluded for reasons of doubt concerning the delirium diagnosis or history of cognitive dysfunction of the patients. In three patients it was not possible to retrieve information of the relatives and in two patients there was some doubt concerning the delirium diagnosis (in both cases the CAM-ICU was negative). In total, 100 patients were included for this study, of whom 50 patients were delirious during the ICU stay and 50 patients were not delirious during the ICU stay. No statistically significant differences in demographic variables and several clinical covariates related to delirium were observed between groups of 50 delirious and 50 nondelirious patients (Table 1). No difference was noted between both groups regarding the moment of blood withdrawal counted from ICU admission (Table 1).

Several pro- and antiinflammatory cytokines, PCT as marker of inflammation, stress response hormone cortisol, as well as several brain specific proteins differed significantly between delirious and nondelirious patients (Table 2).

Table 1 **Demographic variables of delirium and nondelirium ICU-patients**

	Delirium (n=50)	Nondelirium (n=50)	p value
Age in years (95%CI)	72 (38-86)	68 (31-84)	*.10*
Gender (male, N %)	27 (46)	26 (40)	*.50*
Medical patients (N,%)	14 (28)	13 (26)	*.50*
Unplanned admissions (N,%)	23 (46)	7 (35%)	*.34*
APACHE-II score (point) (95%CI)	16 (9-25)	15 (6-23)	*.11*
Inflamed patients (N, %)	26 (52)	20 (40)	*.16*
Days on the ICU (median [IQR] before draw blood	1 [1-2]	1 [1-3]	*.38*
Mean arterial blood pressure in mmHg (95%CI)	64 (47-90)	65 (50-105)	*.37*
Use of sedatives (midazolam, propofol) (N,%)	28 (56)	16 (32)	*.13*
Use of opiates (N,%)	45 (90)	42 (84)	*.28*
Urea in mmol/L (95%CI)	11 (4-29)	9 (4-23)	*.14*
Metabolic acidosis (N,%)	15 (30)	14 (28)	*.50*

Data are expressed as mean and standard deviation (±) unless other reported.

Of note, all measured levels of biomarkers were well above the lower detection limit. Differences in biomarkers between inflamed and noninflamed delirious patients are illustrated in Additional file.

Inflamed patients

This group consisted of 26 delirium and 20 nondelirium ICU patients. Several pro- as well as antiinflammatory cytokines, PCT and cortisol were significantly higher in the delirium group compared to the nondelirium group (Table 3). Levels of brain specific proteins were comparable between the groups, except for a borderline significant elevated level of S100-β in the delirium group (p=0.07). In univariate logistic regression analysis IL-8, MCP-1, PCT, cortisol, and S100-β were significantly ($p < .05$) associated with delirium. Extended with the biomarkers TNF-α, IL-6, IL-18, IL-1ra and IL-10 the 10 best biomarkers associated with delirium (all $p < .10$) were then entered into a multivariate logistic regression analysis. This multivariate analysis demonstrated a significant association between the proinflammatory cytokine IL-8 (odds ratio 9.0; 95%CI 1.8-44.0) with the presence of delirium in inflamed patients.

Noninflamed patients

This group of patients consisted of 24 delirium and 30 nondelirium ICU patients. The proinflammatory cytokines IL-6 and IL8 as well as the antiinflammatory cytokines IL-1ra and IL-10 and level of PCT were significantly higher in delirious patients compared with the nondelirious patients. Furthermore several amyloidβ forms differed significantly, and Tau levels differed borderline significant between the two groups (Table 3).

Biomarkers that were significantly associated with delirium were IL-8, IL-1ra, IL-10, ratio Aβ1-42/40 and ratio AβN-42/40. Furthermore IL-6, PCT, cortisol, ratio Tau/Aβ1-42, Aβ1-40 and AβN-40 were in total the 10 best with delirium associated biomarkers (all $p < .10$) in univariate logistic regression analysis. Multivariate logistic regression analyses with these biomarkers showed a significant association of ratio Aβ-42/40 (OR 0.03; 95%CI 0.002 - 0.50) and the antiinflammatory cytokine IL-10 (OR 2.6; 95%CI 1.1 - 5.9) with the presence of delirium in noninflamed patients.

Correlations of biomarkers with long-term subjective cognitive failure

At a median of 18 months after ICU discharge, 10 out of the 100 ICU patients had died. Except for a significantly lower level of IL-1β in the survivors group, no other differences were found between the survivors and nonsurvivors (data not shown).

Table 2 **Differences between delirious and nondelirious patients**

	Delirium (n=50)		Nondelirium (n=50)		Differences p value
Proinflammatory cytokines					
TNF-α (pg/mL)	11	[7-14]	8	[5-13]	*.02**
IL-1β (pg/mL)	3	[3-6]	3	[3-7]	*.63*
IL-6 (pg/mL)	61	[37–113]	37	[23-81]	*.01**
IL-8 (pg/mL)	29	[20–39]	17	[9–26]	*< .0001**
IL-17 (pg/mL)	3	[3-4]	3	[3-4]	*.17*
IL-18 (pg/mL)	99	[74–161]	86	[70–120]	*.11*
MIF (pg/mL)	418	[300-724]	257	[157–576]	*.02**
Antiinflammatory cytokines					
IL-1ra (pg/mL)	36	[17–68]	21	[13–33]	*.001**
IL-10 (pg/mL)	29	[16–51]	18	[9-39]	*.01**
Chemotactic cytokines					
MCP-1 (pg/mL)	372	[248–589]	239	[179–325]	*< .0001*
Defensin					
HNP (µg/mL)	0.06	[0.03–0.12]	0.06	[0.03–0.10]	*.89*
Markers of inflammation					
CRP (mg/ml)	56	[35-114]	47	[32-84]	*.11*
Procalcitonine (ng/mL)	0.35	[0.17-1.68]	0.14	[0.07–0.36]	*< .0001**
Stress response hormone					
Cortisol (µmol/L)	0.51	[0.31–0.97]	0.35	[0.09-0.62]	*.006**
Brain Specific Proteins					
S100-β (pg/ml)	132	[100–294]	135	[90-219]	*.40*
Tau (pg/ml)	41	[24–91]	32	[17-56]	*.07*
Ratio Tau/A$\beta_{1\text{-}42}$	1.14	[0.62-2.71]	0.95	[0.47-1.69]	*.10*
A$\beta_{1\text{-}42}$ (pg/ml)	36	[29-47]	36	[30-41]	*.70*
A$\beta_{1\text{-}40}$ (pg/ml)	156	[129–225]	146	[113-163]	*.05*
Ratio A$\beta_{1\text{-}42/40}$	0.23	[0.20-0.27]	0.25	[0.23-0.30]	*.006**
A$\beta_{N\text{-}42}$ (pg/ml)	31	[23-40]	29	[24-36]	*.65*
A$\beta_{N\text{-}40}$ (pg/ml)	222	[167-276]	178	[146-220]	*.02**
Ratio A$\beta_{N\text{-}42/40}$	0.15	[0.12-0.17]	0.17	[0.14-0.19]	*.04**
Ratio A$\beta_{1\text{-}42/N\text{-}42}$	1.26	[1.03-1.34]	1.29	[1.10-1.40]	*.48*
Ratio A$\beta_{1\text{-}40/N\text{-}40}$	0.78	[0.69-0.85]	0.80	[0.73-0.92]	*.28*

*Data are expressed as median and IQR. Differences were tested with Mann-Whitney U-test. * p-value < .05*

In total, 52 (58%) patients out of the 90 survivors returned the CFQ, 23 (44%) of these were delirious during their ICU stay. No important differences were noted between nonresponders and responders concerning age (69±8 versus 73±6; p = .12), APACHE-II (16±3 versus 15±4; p = .31), gender (male 46% versus 54%; p = .45), delirium (46% versus 44%; p = .60) and inflamed (55% versus 40%; p = .29).

Table 3 **Differences between delirium and nondelirium patients in inflamed and noninflamed patients**

	Inflamed (n=46)				Noninflamed patients (n=54)				
	Delirium (n=26)		Nondelirium (n=20)		p-value	Delirium (n=24)		Nondelirium (n=30)		p-value
Proinflammatory cytokines										
TNF-α (pg/mL)	13	[10-16]	11	[5-18]	*.17*	8	[5-13]	7	[5-11]	*.18*
IL-1β (pg/mL)	3	[3-6]	4	[3-17]	*.67*	3	[3-6]	3	[3-6]	*.69*
IL-6 (pg/mL)	73	[38–143]	41	[21-90]	*.09*	50	[29–90]	34	[22-64]	*.047**
IL-8 (pg/mL)	31	[24–44]	17	[9–26]	*<.001**	20	[12–32]	14	[9–22]	*.001**
IL-17 (pg/mL)	4	[3-7]	3	[3-6]	*.22*	3	[3-4]	3	[3-3]	*.63*
IL-18 (pg/mL)	136	[88–187]	84	[65–132]	*.03**	82	[66-141]	88	[72–120]	*.54*
MIF (pg/mL)	438	[294–796]	257	[157–576]	*.13*	334	[214–561]	249	[179–702]	*.08*
Antiinflammatory cytokines										
IL-1ra (pg/mL)	48	[27–74]	32	[18–47]	*.04**	24	[17–51]	16	[11–25]	*.02**
IL-10 (pg/mL)	23	[13–47]	13	[5-35]	*.08*	28	[12–44]	22	[9-46]	*.03**
Chemotactic cytokines										
MCP-1 (pg/mL)	516	[295–822]	251	[199–339]	*.001**	268	[192–398]	233	[175–306]	*.15*
Defensin										
HNP (µg/mL)	0.06	[0.03–0.13]	0.07	[0.03–0.09]	*.60*	0.06	[0.04–0.10]	0.04	[0.03–0.10]	*.51*
Markers of inflammation										
CRP (mg/ml)	84	[56-190]	84	[43-140]	*.40*	42	[29-65]	41	[27-64]	*.44*
Procalcitonine (ng/mL)	1.0	[0.23-2.0]	0.28	[0.10–0.64]	*.003**	0.22	[0.11-0.55]	0.12	[0.06–0.18]	*.01**
Stress response hormone										
Cortisol (µmol/L)	0.59	[0.34–0.98]	0.48	[0.18-0.61]	*.06*	0.46	[0.23–0.72]	0.30	[0.06-0.66]	*.06*
Brain Specific Proteins										
S100-β (pg/ml)	172	[113–409]	134	[88-163]	*.07*	128	[87–210]	136	[92-247]	*.60*
Tau (pg/ml)	42	[26–131]	43	[24-75]	*.56*	40	[21-78]	27	[17-46]	*.08*
Ratio Tau/A$\beta_{1\text{-}42}$	1.03	[0.62-3.45]	1.12	[0.40-2.21]	*.68*	1.17	[0.60-2.52]	0.90	[0.48-1.26]	*.07*
A$\beta_{1\text{-}42}$ (pg/ml)	41	[31-52]]	38	[31-42]	*.36*	34	[26–43]	36	[30-42]	*.55*
A$\beta_{1\text{-}40}$ (pg/ml)	158	[132–229]	155	[137-178]	*.55*	148	[109–223]	129	[106-158]	*.08*
Ratio A$\beta_{1\text{-}42/40}$	0.23	[0.20-0.28]	0.24	[0.22-0.26]	*.72*	0.22	[0.19–0.26]	0.26	[0.23-0.33]	*.001**
A$\beta_{N\text{-}42}$ (pg/ml)	31	[26-43]	29	[24-39]	*.57*	28	[20-37]	28	[24-35]	*.79*
A$\beta_{N\text{-}40}$ (pg/ml)	200	[167-283]	184	[147-229]	*.24*	225	[168-273]	178	[145-220]	*.04**
Ratio A$\beta_{N\text{-}42/40}$	0.16	[0.13-0.18]	0.18	[0.12-0.19]	*.47*	0.13	[0.10-0.17]	0.16	[0.14-0.20]	*.02**
Ratio A$\beta_{1\text{-}42/N\text{-}42}$	1.28	[1.00-1.39]	1.31	[1.18-1.48]	*.26*	1.24	[1.04-1.33]	1.23	[1.05-1.39]	*.90*
Ratio A$\beta_{1\text{-}40/N\text{-}40}$	0.82	[0.74-0.89]	0.89	[0.73-0.96]	*.27*	0.72	[0.65-0.84]	0.76	[0.70-0.87]	*.35*

*Data are expressed as median and IQR. Differences were tested with Mann-Whitney U-test. * p-value < .05*

We found no correlation between S100-β, total human Tau, cortisol or any of the other measured inflammatory mediators, CFQ, age, APACHE-II score, and mean blood pressure. In addition, we found no correlations between CFQ and age, APACHE-II score and length of stay in the ICU.

The patient number per subgroup were too low and therefore did not allow us to perform correlation analyses between biomarkers and the different subgroups for reasons of lack of statistical power.

Discussion

This study shows that differences exist in various inflammatory mediators associated with delirium between inflamed and noninflamed patients. After multivariate regression analysis, IL-8 was associated with delirium in inflamed patients, whereas in noninflamed patients, IL-10 and Aβ-42/40 were associated with delirium. These differences between inflamed and noninflamed ICU patients in delirium-associated biomarkers suggest that the underlying mechanism governing the development of delirium in inflamed patients differs from that in noninflamed patients. Furthermore, we demonstrated that, in contrast to inflammatory mediators, different forms of amyloidβ significantly correlate with long-term subjective cognitive problems in ICU patients, illustrating that the underlying mechanism of delirium is relevant for its long-term cognitive consequences.

This is the first study investigating plasma amyloidβ (Aβ) levels and human Tau in critically ill patients in relation to the presence of delirium. In view of the reported increased incidence of dementia following ICU/hospital admission (16), our findings could provide a possible mechanistic link, because noninflamed delirium is associated with Aβ, but this must be confirmed in a longitudinal study focusing on these biomarkers combined with more-extensive cognitive testing. Furthermore, Aβ is associated with sustained long-term subjective cognitive dysfunction in ICU patients. Studies comparing plasma levels of Aβ between Alzheimer (AD) and non-Alzheimer dementia patients and controls (17;18;32) have yielded conflicting results with respect to levels of different forms of Aβ. Increased levels of Aβ1-42 (17) as well as increased levels of Aβ1-40 (18) were found in dementia patients (32). In addition, increased levels of Tau/Aβ1-42 ratio have been found in cerebrospinal fluid (CSF) of patients with cerebral amyloid deposition (33), but this has not yet been investigated in plasma. In the present study, the difference in levels of total Tau and the Tau/Aβ1-42 ratio between noninflamed delirious patients and noninflamed nondelirious patients approached statistical significance. It is known that plasma levels of Aβ are age dependent (34), however, this could not have confounded our results because

there were no differences in age between delirious and nondelirious patients in our study. Additionally, the patients investigated in this study were not recognized with a history of cognitive impairment by patients' medical history and information from their relatives, which could explain differential Aβ levels. The lower Aβ1-42/40 ratio, probably due to an increase of Aβ1-40 at a constant Aβ1-42 level, in combination with a significant correlation with long-term cognitive failure on several domains of the CFQ are in accordance with findings that elevated levels of Aβ1-40 increases the risk of developing dementia (16;18). Importantly, this finding of early lower Aβ1-42/40 ratio and ratio Aβ1-40/N-40 in delirious patients without signs of serious previous cognitive impairment is tempting to speculate that this represents the first sign of an imbalance in the Aβ metabolism. To our knowledge, these early findings of imbalance in Aβ metabolism have not been reported before. Our findings might therefore shed new light on the important question whether delirium plays a causative role in the development of dementia in later life, or if delirium is the first sign of dementia. Because deposition of Aβ in the brain is generally considered to be a long-term process and samples in our study were drawn shortly after the onset of delirium, it is more plausible that delirium may be the first sign of an early dementia process. However, a cause-effect relationship cannot be determined in a cross sectional observational study like ours. This hypothesis of early imbalance in Aβ metabolism in delirious patients need to be confirmed in future studies.

Previously, it has been demonstrated that delirium is associated with elevated levels of IL-6, IL-8 and S100-β in non-ICU patients (9;10) and with IL-6 and S100-β in septic ICU patients (13). IL-8 levels were not measured in these septic patients. We showed, by using a multivariate logistic regression analysis, that levels of IL-8 in inflamed patients were associated with delirium but IL-6 was not. A possible reason for this discrepancy might be that we determined biomarkers directly after the first positive delirium screening, whereas it has been shown that the highest levels of IL-6 occur in the later phase of delirium (10).

Several limitations of our study should be addressed. First, we used the CAM-ICU to diagnose delirium in ICU patients instead of the gold standard: the DSM-IV criteria (35). It is recognized that it is not feasible to use this gold standard in ICU patients, and therefore the CAM-ICU is an accepted alternative to diagnose delirium in the ICU. The CAM-ICU has the highest sensitivity and specificity rate of all delirium assessment tools (36;37) and is well implemented in the daily practice of our nurses with a high interrater reliability (26). In addition, to strengthen the delirium diagnosis, all medical and nurse files of the patients were analyzed, and patients were not included when in doubt of the delirium diagnosis. Second, we did not use a validated cognitive assessment tool such as the informant questionnaire on cognitive decline short form (IQCODE-sf), which is a surrogate evaluation to determine if the patient suffered from serious

cognitive impairment prior to ICU admission. Instead of this, we used information from medical records and the next of kin of the patients to identify whether the patient had a history of cognitive impairment. In case of any reference to or sign of cognitive impairment, patients were not included in our study. Furthermore, as a measure of patients' cognitive function 18 months after ICU discharge, we used the validated CFQ, which is a self-evaluated questionnaire to detect cognitive-based failures and not dementia and is also not a specific psychometric test, which may result in more-objective data. Although this can be considered a limitation of our study, our findings are the results of patient's own perception of cognitive functioning and are therefore informative and relevant. Third, in this study we measured biomarkers only at one point in time. In a longitudinal biomarker study (9), a difference in cytokine levels before and during delirium was found. In the absence of biomarker data in critically ill patients with delirium, we chose to perform an exploratory study to investigate which biomarkers were most strongly associated with delirium immediately after the onset of delirium. This was an exploratory hypothesis-generating study, of which the results may facilitate hypotheses for future research. Fourth, potential covariates need to be considered as a potential limitation of the study, in contrast to a randomized trial in which possible covariates are likely to be equally divided between the groups. Although baseline patient characteristics were comparable between the delirium and nondelirium groups, unbalanced influence of covariates cannot be ruled out in such an observational study as we performed. Last, we measured levels of brain biomarkers in peripheral blood and not directly in material derived from the brain or cerebrospinal fluid. It is recognized that levels of Aβ1-42 in cerebrospinal fluid of AD-patients are decreased (38), but studies on plasma Aβ forms have yielded ambiguous results (18;39-43). A large prospective study showed that increased plasma levels of Aβ1-40 increased the risk for dementia, especially when the concentration of Aβ1-42 was increased (18). This results in a decrease of ratio Aβ1-42/40 (40). A combination of different brain specific proteins, such as a combination of Aβ with Tau concentrations in CSF, improves discrimination between AD patients and controls (44). Although it has been recommended to determine these biomarkers in CSF rather than in plasma (45), our results are in accordance with these findings. Interestingly, levels of Tau, ratio Tau/Aβ1-42, and Aβ1-40 were increased in inflamed delirious and nondelirious patients and in delirious noninflamed patients, but appear to be lower in nondelirious noninflamed patients. It can be argued that a blood barrier change during systemic inflammation may play a role. This may also suggest that determining neuronal biomarkers in plasma can be used instead of only CSF samples. Obviously, CSF samples are not routinely obtained in our ICU patients. To our knowledge, a study investigating the correlation between CSF and plasma levels of Aβ has yet to be performed.

Conclusion

In inflamed patients, the proinflammatory cytokine IL-8 was independently associated with delirium, whereas in noninflamed patients, the ratio Aβ1-42/40 and IL-10 were independently associated with delirium, as determined by multivariate regression analyses. This suggests that the underlying mechanism governing the development of delirium in inflamed patients differs from that in noninflamed patients. These findings illustrate the relevance of distinguishing between inflamed and noninflamed when investigating biomarkers in delirious patients. Finally, elevated levels of amyloidβ correlated with long-term cognitive impairment. These findings are in line with the notion that delirium in noninflamed ICU patients may represent the first sign of a (subclinical) dementia process. Future research into the relation of delirium, amyloid forms, and long-term cognitive function should include more-extensive tests of cognitive function.

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Additional file

Differences between inflamed and noninflamed delirium patients

	Delirium patients				
	Inflamed (n=26)		**Noninflamed (n=24)**		**p-value**
Proinflammatory cytokines					
TNF-α (pg/mL)	13	[10-16]	8	[5-13]	*.03**
IL-1β (pg/mL)	3	[3-6]	3	[3-6]	*.61*
IL-6 (pg/mL)	73	[38–143]	50	[29–90]	*.58*
IL-8 (pg/mL)	31	[24–44]	20	[12–32]	*.04**
IL-17 (pg/mL)	4	[3-7]	3	[3-4]	*.15*
IL-18 (pg/mL)	136	[88–187]	82	[66-141]	*.004**
MIF (pg/mL)	438	[294–796]	334	[214–561]	*.66*
Antiinflammatory cytokines					
IL-1ra (pg/mL)	48	[27–74]	24	[17–51]	*.02**
IL-10 (pg/mL)	23	[13–47]	28	[12–44]	*.15*
Chemotactic cytokines					
MCP-1 (pg/mL)	516	[295–822]	268	[192–398]	*.01**
Defensin					
HNP (µg/mL)	0.06	[0.03–0.13]	0.06	[0.04–0.10]	*.72*
Markers of inflammation					
CRP (mg/ml)	84	[56-190]	42	[29-65]	*.002**
Procalcitonine (ng/mL)	1.0	[0.23-2.0]	0.22	[0.11-0.55]	*< .0001**
Stress response hormone					
Cortisol (µmol/L)	0.59	[0.34–0.98]	0.46	[0.23–0.72]	*.44*
Brain Specific Proteins					
S100-β (pg/ml)	172	[113–409]	128	[87–210]	*.09*
Tau (pg/ml)	42	[26–131]	40	[21-78]	*.35*
Ratio Tau/A$\beta_{1\text{-}42}$	1.03	[0.62-3.45]	1.17	[0.60-2.52]	*.84*
A$\beta_{1\text{-}42}$ (pg/ml)	41	[31-52]	34	[26–43]	*.07*
A$\beta_{1\text{-}40}$ (pg/ml)	158	[132–229]	148	[109–223]	*.45*
Ratio A$\beta_{1\text{-}42/40}$	0.23	[0.20-0.28]	0.22	[0.19–0.26]	*.31*
A$\beta_{N\text{-}42}$ (pg/ml)	31	[26-43]	28	[20-37]	*.23*
A$\beta_{N\text{-}40}$ (pg/ml)	200	[167-283]	225	[168-273]	*.94*
Ratio A$\beta_{N\text{-}42/40}$	0.16	[0.13-0.18]	0.13	[0.10-0.17]	*.04**
Ratio A$\beta_{1\text{-}42/N\text{-}42}$	1.28	[1.00-1.39]	1.24	[1.04-1.33]	*.64*
Ratio A$\beta_{1\text{-}40/N\text{-}40}$	0.82	[0.74-0.89]	0.72	[0.65-0.84]	*.03**

Data are expressed as median and IQR. Differences were tested with Mann-Whitney U test
** p-value < .05*

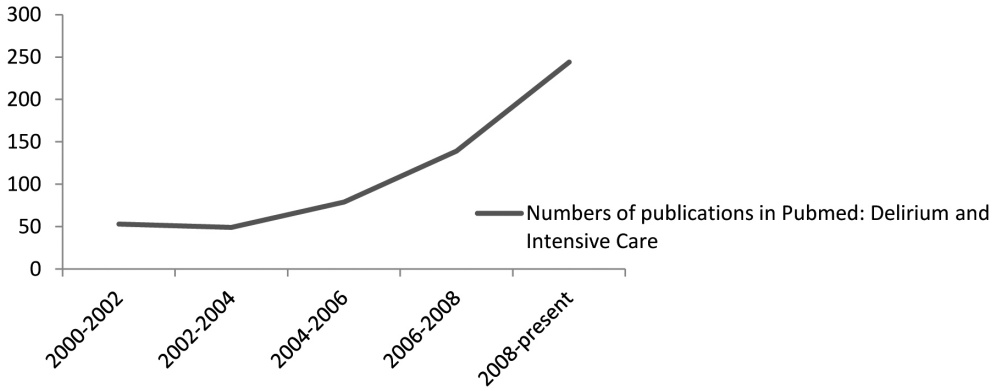
12

General discussion, Conclusions, Future directives

Delirium in Intensive Care Patients

Delirium in critically ill patients is receiving more and more attention, as illustrated by an almost exponential increase in the number of scientific publications (Figure 1). This thesis investigated several missing gaps and in this final chapter we will discuss our findings in view of other studies, discuss possible pitfalls and give directions for future research.

Figure 1 **Numbers of publications in Pubmed: 'Delirium AND Intensive Care'**



In this thesis, we showed and confirmed that the incidence of delirium in critically ill patients is high and associated with serious short- and long-term health-related problems.

In the following discussion we will subsequently focus on the detection of delirium, the clinical impact of delirium, the possibilities for early prediction and prevention and the role of biomarkers.

Detection of Delirium in Intensive Care Patients

The gold standard to diagnose delirium is examination by a psychiatrist, neurologist, or geriatrician using the DSM-IV criteria (1), but in daily clinical ICU practice ICU nurses assess patients for delirium using validated delirium assessment tools. Although the performance of the most frequently used delirium assessment tool, the CAM-ICU, in original validation studies was excellent (2;3) using the CAM-ICU is no guarantee that every patient with delirium will be detected. An important potential reason for this is suboptimal screening by the nurses. To achieve an

optimal performance of the CAM-ICU it is therefore important to first determine barriers and facilitators for successful implementation and second, to use a tailored evidence based implementation strategy as described in chapter 2 (4). In our study we found that lack of delirium knowledge and general availability of the screening tool were the main barriers and that leadership, education and the use of key-nurses played the most important role in our successful implementation. Importantly, this is a single centre study implying that the content of the interventions is likely to be different in other centres. It is further appears imperative that the attending intensivist evaluates the results of the assessment several times a day and results in clinical consequences (5).

Recent studies suggest that the CAM-ICU has a lower performance, in particular a lower sensitivity (5-7) in daily ICU practice. Despite this limitation, we also used the CAM-ICU to determine if patients were delirious or not. However, we additionally screened all medical and nursing files daily for signs of delirium (8) to confirm the diagnosis. Moreover, our delirium diagnosis was based on all CAM-ICU screenings during patients' complete ICU stay, increasing the sensitivity of the test. Therefore, we believe we have not underestimated the number of patients with delirium in our studies.

Even though the performance of the CAM-ICU is lower than in the original validation studies (2;3), it is still superior to that of an observational assessment tool such as the ICDSC (7). However, there is a clear need for further improvement. Notably, there are clear indications that early recognition (4) and treatment (9) of delirium could be beneficial for an individual patient supporting the importance of early detection.

There are several possibilities that, besides the compliance of the nurses to assess the patients for delirium, could improve the performance of delirium detection. The fluctuating course of delirium can be missed by the testing tools when the screening is performed in between periods of confusion. This issue becomes even more relevant when patients are screened less frequently, e.g. twice a day instead of three times a day. It appears likely that an observational tool, such as the Intensive Care Delirium Screening Checklist (ICDSC) (10) does not have this problem or at least to a lesser extent, as the observational period covers a longer period of time, most frequently one shift of 8 hours. However, some features such as attention and disorganized thinking are difficult to detect by observation alone and may therefore be easily missed by nurses, explaining the relatively low specificity of this test (10). A combination of the CAM-ICU and ICDSC could enhance the performance of delirium detection, but this has not been investigated yet.

Apart from the screening tools, other ways to diagnose delirium would be helpful. We explored the possibility to detect specific markers for the diagnosis of delirium in

urine (using a proteomics technique), but were unable to find a specific fingerprint (11). This may be explained by the multifactorial pathogenesis of delirium (12-14). Another interesting area that warrants further study is to examine whether electroencephalography (EEG) of delirious patients shows specific abnormalities. In patients suffering from sepsis-associated delirium specific EEG abnormalities have been observed (15) and similar abnormalities were found in small studies in medical and trauma patients with delirium as well (16). How these findings may facilitate delirium diagnosis needs to be further explored. Naturally it is not feasible to perform electroencephalography in all intensive care patients continuously. Perhaps, when typical EEG abnormalities for delirium are found, a specific EEG algorithm could be developed resulting in a less labor intensive EEG method that is more suitable to use in daily practice. Another approach to detect delirium in the future could be the development of a movement algorithm for motor activity patterns that may be typical for delirium (17-19). These patterns were recently studied using on-body-accelerometers (20-25). Importantly, the used accelerometers, such as the Actiwatch, have the critical disadvantage that they only measure movements of one limb of the body. Video-based actigraphy monitoring may represent a more promising method because of the advantage that altered motions of the whole body can be detected and analysed without additional on-body sensors. Several studies have described the use of computer vision techniques to assess agitation in sedated (ICU) patients (26-28). Currently we are conducting a study with Philips Research to determine if it is possible to build an algorithm that analyses movements and thereby detect delirium using video camera observation.

To summarize, there are various options to improve the detection of delirium. First, to combine a screening tool with an observational assessment tool could improve sensitivity. The best option is likely to combine the CAM-ICU with the ICDSC and to determine the performance of the new tool compared to the CAM-ICU alone. Importantly, this can be done relatively easy and fast, as both methods are currently used in daily practice. Second, to determine whether or not specific EEG abnormalities occur in ICU patients suffering from delirium. If so, an EEG algorithm and development of an electronic device with a limited amount of leads could make this technique feasible for daily clinical practice. Last, the development of an algorithm to automatically analyze movement, obtained by video actigraphy monitoring would be most feasible in daily ICU practice. It is expected that in the nearby future several possibilities to improve the detection of delirium will emerge that will improve the sensitivity and specificity of the diagnostic tools, and simultaneously will be less labor-intensive for caregivers than performing the current screening tests.

Impact of Delirium in Intensive Care Patients

In chapter 5 we showed that delirium is associated with a poor outcome (29) and these findings confirm previous findings that delirium is associated with several important health consequences, such as prolonged duration of mechanical ventilation, ICU and hospital length of stay, higher incidence of re-intubations, accidental removal of tubes and catheters and ICU re-admissions (30-32). Furthermore, in chapter 5 and 6 we determined that delirium is also associated with an increased mortality rate (29;33) which also confirms earlier findings (34;35). Despite the fact that our large cohort studies were performed in a single university hospital population, the comparability to earlier findings supports the generalizability of our findings. Except for one study (34), all previous studies adjusted for the severity of illness. However, most investigators, including us, used the Physiology and Chronic Health Evaluation-II (APACHE) score, which is a static severity of illness variable using only data collected within the first 24 hours after ICU admission. This implies that deterioration of patients' health condition during his/her ICU stay is not taken into account. Whether poor outcome is a result of delirium or must be considered as an epiphenomenon of severity of illness needs to be studied more extensively, as without a dynamic severity of illness variable, it remains unclear if deterioration of patients' health is directly due to the development of delirium or not. Therefore, we recommend to include a dynamic parameter such as the sequential organ failure assessment (SOFA) score (36) as a covariate in future delirium-associated outcome studies to obtain more insight in the course-effect relationship. As determined in chapter 6, adding delirium to the static mortality prediction model APACHE-II did not result in improvement of its performance (33) but it still needs to be studied if adding delirium to a dynamic model could improve its performance.

Future research should also focus on radiological imaging of the brain in patients suffering from delirium. New techniques may be helpful to determine the relation between the severity of brain damage and delirium in general and more specific in its subtypes. Recently, a small study of eight patients showed lesions in the white matter of the brain using magnetic resonance imaging (MRI) techniques in ICU patients suffering from delirium (37). This is a first step that needs follow-up in more and larger studies. Imaging studies could be helpful to elucidate if short-term poor outcome is a direct result of brain damage related to delirium or is the result of secondary deterioration. In addition, imaging could also be useful in long-term follow-up studies. We demonstrated in chapter 7 that delirium is associated with long-term cognitive problems and that these problems are related to the duration of delirium (38). Although we did not take into account changes in disease severity over time, we did adjust for length of stay in the ICU as we assumed that this can be

considered as a surrogate measure for a dynamic severity of illness score. While we did not find differences in long-term health related quality of life (HRQoL) outcome between ICU survivors that suffered from delirium during their ICU stay and those who did not, it would be interesting to determine HRQoL more frequently over time once patients are discharged from the ICU. Other studies showed differences in HRQoL between delirious and non-delirious ICU survivors after 12 months (39) and recovery of cognition when measured over time (40). Our cognitive outcome results were in line with another cognitive impairment study (40), indicating that long-term cognitive impairment following ICU treatment is an issue of importance. Therefore, it would be of interest to obtain questionnaires immediately after ICU admission and repeatedly thereafter during follow-up to acquire more insight into the effects of delirium on the course of cognitive dysfunction over time. Since it is time consuming and may also be burdensome for the patient to use a validated self-evaluating cognitive questionnaire, the cognitive failure questionnaire (41) is a good alternative. To estimate the quality of life of a patient at ICU admission, it has been shown that patients' relatives can reliably act as a surrogate to fill in a HRQoL questionnaire on behalf of the patient (42). For testing patients' cognitive function at the time of ICU admission the Informant Questionnaire on Cognitive Decline-short form (IQCODE) (43) could be used for this purpose. Currently we are performing a long-term follow-up HRQoL study with repeated measurements starting immediately after ICU admission using the IQCODE and the CFQ during the follow-up.

Prediction and Prevention of Delirium in Intensive Care Patients

The short- and long-term consequences of ICU acquired delirium make adequate prevention imperative. The first step for effective prevention is to identify high risk patients. In chapter 8 we described the development and validation of a delirium prediction model (44). This prediction-of-delirium-in-ICU-patients (PREDELIRIC) model uses covariates that are readily available within 24 hrs following ICU admission and exerts a high predictive value, to predict delirium for the complete ICU length of stay. We validated this model in several hospitals in The Netherlands and showed that the predictive value remained good. However, due to treatment differences, generalizability to other countries is still not possible. At the moment we are therefore conducting an international validation study in several countries in Europe and also in Australia. Although the model is able to predict delirium 24 hours after ICU admission for the complete ICU stay, patients who develop delirium during the first day could therefore be missed with this model. An early prediction model

that predicts delirium immediately after ICU admission would be useful. Together with the international validation study we are also collecting data of important risk factors immediately after ICU admission to develop and to validate an 'early prediction model' (E-PREDELIRIC). Another point that needs to be addressed is that the PREDELIRIC model is a static model, meaning that the predicted chance to develop delirium does not change when patients' condition deteriorates during the ICU admission. Adjustments of the PREDELIRIC model using early available factors and dynamic data during the ICU stay may further improve the predictive value of the model.

After the PREDELIRIC model was developed and validated the model was implemented in our daily clinical practice. This enabled us to identify patients with a high risk for the development of delirium. We decided to use the model to standardize our delirium prevention policy and to treat patients with an estimated risk to develop delirium of 50% or more, and patients with a history of dementia or alcohol abuse with a low dose of haloperidol. We decided in advance to evaluate the results after one year. The effects were compared with a historical control group and a contemporary group of patients who did not receive haloperidol prophylaxis, mainly during the implementation phase. The results of this case control study are described in chapter 9 (45) showing beneficial effects of haloperidol prophylaxis and additionally confirming that the use of a delirium prediction model can help to identify high risk patients and focus our preventive measures on those patients that need it most. Unfortunately, the design of the study does not provide the highest level of evidence. The next step should be to confirm the results in a double-blinded randomized controlled trial in order to abandon possible bias, such as selection bias. Currently we are preparing this multicenter trial. Because, despite prophylaxis, the incidence of delirium was still rather high and given the few side-effects of low dose haloperidol, we are planning to also investigate the effect of a higher prophylactic dosage of haloperidol in a third arm of this trial. In the mean time, we are also developing a "delirium in intensive care app." for smart phones and for the iPad to further facilitate use of the PREDELIRIC model in daily practice.

Apart from pharmacological interventions, focus on non-pharmacological nursing interventions and on the ICU environment is also warranted. Concerning nursing interventions it has been shown that a program focusing on several risk factors, including cognitive impairment, sleep deprivation and immobility, resulted in a reduction of the delirium incidence and duration of delirium in non-ICU patients with a mediate or high risk for delirium (46). Nursing interventions aiming for early mobilization of mechanically ventilated intensive care patients resulted in a reduced duration of delirium (47). This promising area needs to be studied in ICU patients in the future.

Another interesting area that needs to be studied is the effect of restoring the circadian rhythm, since it is recognized that delirium is often accompanied by disruption of the sleep-wake cycle (18). Melatonin, a hormone that is produced in the pineal gland mainly during the night, plays an important role in the regulation of the sleep-wake cycle (48). Exogenous treatment with melatonin resulted in a reduction of delirium in elderly non-ICU patients (49), but its effectiveness in ICU patients is not sufficiently studied yet (50). Another approach to affect the circadian pacemaker is the use of artificial light. Interestingly, it has been determined that in patients nursed in a room with a lack of daylight the chance to develop delirium is more than doubled (51). Artificially influencing the environmental light could therefore be effective in the prevention of delirium or reducing its negative effects on patients' health. This interesting area needs to be studied in the ICU setting. At this moment we are studying the effect of applying artificial light on the delirium incidence and other delirium related outcome measures.

Role of Biomarkers related to Delirium in Intensive Care Patients

There is an acronym that is used to memorize the different causes of delirium: I WATCH DEATH (see textbox) of which the first letter 'I' stands for 'Infection'. We showed that in patients with an infection present at the time of ICU admission the chances of becoming delirious are more than tripled compared to non-infectious patients (44). When the presence of infection during patients' complete ICU admission is taken into account, the chance to develop delirium is even 18 times higher (52).

Acronym 'I watch Death' for causes of Delirium

I Infections
W Withdrawal
A Acute metabolic diseases
T Trauma
C Central Nervous System
H Hypoxia
D Deficiencies
E Endocrinopathies
A Acute Vascular
T Toxins or Drugs
H Heavy metals

In chapter 10 we examined the role of systemic inflammation and the related increase in inflammatory biomarkers on brain function and cognition in the human endotoxemia model (53). Experimental endotoxemia results in both increases in inflammatory markers and in stress hormones (54). Therefore, the model could lead to stress hormone-related increased alertness, or to the first signs of encephalopathy as observed in septic patients. Although the human endotoxin model mimics the pathophysiological changes of septic patients in many ways (55-57), we showed that this short-term systemic inflammation model did not provoke the occurrence of septic encephalopathy. Therefore the model seems unsuitable to further study the onset of inflammation-induced delirium.

Administration of a high dosage of endotoxin in prion-diseased rodents resulted in delirium-like symptoms but this did not occur in rodents without a neurodegenerative disease (58). These results suggest that delirium predominantly occurs in inflamed patients with an underlying disease.

In chapter 11 we studied the association of various markers of inflammation and brain specific proteins with delirium in patients in the presence or absence of infection/SIRS criteria and their relation to long-term cognitive function (59). While in other studies it was determined that several cytokines (60;61) and also the brain specific protein S100-β (a marker for astrocyte damage) (62) were associated with delirium, these studies were performed in non-ICU patients. In addition, no distinction was made between infectious and non-infectious delirious patients. Patients who suffered from delirium during their hospital stay have an increased risk for dementia on the long-term (63). This raises the question which one comes first; delirium as the first sign of a subclinical dementia syndrome, or dementia as a long-term consequence of brain damage evoked by delirium. It is known that patients with dementia have increased plasma levels of some amyloidβ forms (64-66) and increased levels of Tau/Aβ1-42 ratio in cerebrospinal fluid (67). We showed that it is relevant to distinguish between ICU patients with and without inflammation when studying the role of biomarkers in the development of delirium and its long-term cognitive consequences (59).

We found that inflammatory markers were associated with delirium in ICU patients with clinical signs of infection/inflammation, while amyloidβ1-42/40 and the anti-inflammatory cytokine IL-10 was associated with delirium in patients without inflammation. In addition, elevated levels of amyloidβ were associated with long-term cognitive impairment while inflammatory markers were not. This could suggest that in patients with inflammation delirium is a result of the underlying inflammatory process while delirium in patients without inflammation may represent the first sign of a (subclinical) dementia syndrome. However, this complicated issue needs further investigation.

Based on our results future research should focus on these relevant pro- and anti-inflammatory cytokines and brain specific proteins in delirious patients with and without inflammation and measure these biomarkers at the time of ICU admission and serially over time. In addition, combined with serially measured cognitive function or even with radiological imaging, as suggested in part two of this chapter, this may further elucidate the mechanism of the onset of delirium and the long-term consequences on cognitive functioning.

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13

Summary

Summary

Delirium is a psycho-organic disorder with an acute onset, disturbances in consciousness and altered cognition. The term psycho-organic disorder implies that there is always a physical cause such as an infection, dehydration, electrolyte disturbances or renal failure, underlying the onset of delirium. Three subtypes of delirium are described: a hyperactive subtype with symptoms of hyperalertness or agitation, a hypoactive subtype featured with signs of hypoalertness or lethargy and the alternating or mixed subtype, characterized by alternating hyper- and hypoactive symptoms.

This thesis has four main research aims that are addressed in separate parts:

- To gain more insight into the diagnosis of delirium in ICU patients using the confusion assessment tool and to explore if delirium could be diagnosed with tools other than existing delirium assessment tools
- To determine the impact of delirium on several short- and long-term health related consequences
- To determine if delirium in intensive care patients can be predicted and prevented
- To explore the role of (inflammatory) biomarkers in delirium in ICU patients

In **PART ONE** we focussed on the *Detection of Delirium in Intensive Care Patients*. Following a general and background description of delirium in **Chapter 1** we described a tailored strategy to implement the confusion assessment method- ICU (CAM-ICU) in our daily practice focused on potential barriers, using several evidence based implementation interventions in chapter 2. We evaluated our strategy and measured CAM-ICU compliance, interrater reliability, and delirium knowledge as measures for success. Furthermore we compared haloperidol use, as a proxy for delirium incidence, before and after the implementation. In four months, the CAM-ICU compliance, the delirium knowledge of the ICU-nurses, and the interrater reliability increased significantly. In addition, more patients were treated with haloperidol, however with a lower dose and for a shorter period of time. Our conclusion was that using this tailored implementation strategy, the CAM-ICU was successfully introduced in the ICU and the main goals were achieved rapidly. The observation that more patients were treated with haloperidol with a lower dose and for a shorter period of time following the successful implementation of the CAM-ICU suggests that delirium is detected in an earlier phase during which the patient is more sensitive to the treatment with haloperidol.

In **Chapter 3** a multicentre study in the Netherlands was described examining the

performance of the CAM-ICU when used by ICU-nurses in daily practice. Two teams of three delirium experts including psychiatrists, geriatricians and neurologists visited ten ICUs. Based on cognitive examination, inspection of medical files and DSM-IV-TR criteria for delirium, the expert teams classified patients as awake and not delirious, delirious, or comatose. This served as 'gold standard'. The CAM-ICU as performed by the bedside ICU-nurses in 181 patients was compared with the 'gold standard'. We found a lower performance of the CAM-ICU compared to the original validation studies of the CAM-ICU. Although the specificity of the CAM-ICU in all participating ICUs was high, the sensitivity of the CAM-ICU was rather low and there were noticeable differences between the participating ICUs. Furthermore, when stratifying the data, the sensitivity was lowest in the hypoactive delirium subgroup, and the sensitivity was poor in neurocritical care patients. Our finding that the specificity of the CAM-ICU as performed in routine practice appears to be high, but that sensitivity is low hampers early detection of delirium by the CAM-ICU.

In the last chapter of part one, **Chapter 4**, we described a prospective study in which we explored the possibility to find a fingerprint of delirium markers in the urine of patients following cardiac surgery using urinary proteomics. While urinary proteomics has successfully been applied to identify novel biomarkers associated with various disease states, its value in delirious patients was not investigated. For this study cardiac surgery ICU patients who suffered from hyperactive delirium were included and matched with non-delirium patients on relevant variables. Urine was collected within 24 hours after the onset of delirium. Matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) was applied to detect differences in the urinary proteome associated with delirium in these ICU patients. We included 10 hyperactive delirium and 10 meticulously matched non-delirium post-cardiac surgery patients, but no relevant differences in the urinary excretion of proteins were observed. We concluded that MALDI-TOF MS of urine does not reveal a clear hyperactive delirium proteome fingerprint in ICU patients.

PART TWO concentrated on the *Impact of Delirium in Intensive Care Patients* and in **Chapter 5** we determined the overall delirium incidence and duration of delirium, per delirium subtype and per ICU admission diagnosis. Additionally, we determined the short-term consequences of delirium. In a large prospective observational study all adult consecutive patients admitted to our ICU during one year were included. Delirium was assessed using the CAM-ICU and divided in three subtypes: hyperactive, hypoactive and mixed subtype. As measures for short-term consequences we registered duration of mechanical ventilation, re-intubations, incidence of unplanned removal of tubes, length of (ICU) stay and in-

hospital mortality. In total 1,613 patients were included of whom 26% developed delirium. The incidence rates in the neurosurgical (10%) and cardiac surgery group (12%) were the lowest; incidence was higher in medical patients (40%) and highest in neurological patients (64%). The mixed subtype of delirium occurred most frequently and the hyperactive subtype had the lowest incidence in ICU patients. The median duration of delirium was two days and was significantly longer in the mixed subtype. Concerning short-term consequences, delirious patients were more likely to be mechanically ventilated and if so, for longer periods of time, and were more likely to remove their tubes and catheters. Also, they stayed in the ICU and hospital for a longer time, and had a six times higher chance of dying compared to non-delirious ICU patients, even after adjusting for their severity of illness score. We concluded that the delirium incidence in a mixed ICU population is high and differs importantly between ICU admission diagnoses and the subtypes of delirium. Patients with delirium had a significantly higher incidence of short-term health problems, independent of their severity of illness and this was most pronounced in the mixed subtype of delirium.

In **Chapter 6** we examined if adding delirium, present within 24 hours after ICU admission, as an additional variable to the acute physiology and chronic health evaluation (APACHE-II) score, would improve the predictive estimate of the model. In this prospective cohort study 2,116 adult patients were screened for delirium and 1,740 patients were included for analysis of whom 332 (19%) were delirious at the time of ICU admission or within 24 hours after admission. We found that delirium was significantly associated with in-hospital mortality. However, the predictive accuracy of the APACHE-II did not improve after adding delirium, both in the total group as well as in the subgroup excluding cardiac surgery patients. We concluded that, although delirium is a significant predictor of mortality in ICU patients, adding delirium as an additional variable to the APACHE-II model does not improve its predictive estimate.

In **Chapter 7** we examined the impact of delirium on long-term health related quality of life (HRQoL) and cognitive functioning of ICU survivors. In this prospective follow-up study at a median of 18 months after ICU discharge, HRQoL questionnaires were sent to 1292 ICU survivors with (21%) and without (79%) delirium during their ICU stay. We used the short form-36v1 (SF-36), checklist individual strength (CIS-) fatigue and cognitive failure questionnaire (CFQ) to measure patients' perceived HRQoL and cognitive functioning. A total of 915 (71%) patients responded, of which 171 (19%) patients suffered from delirium during their ICU stay. After adjusting for covariates, no differences were found between delirium and non-delirium survivors in the SF-36 and CIS-fatigue scores. However, survivors who had suffered from delirium reported that they made significantly more social blunders and their

overall cognitive function was significantly impaired compared to survivors who had not been delirious. Survivors of mixed type and hyperactive delirium performed significantly worse on the domain mental health compared to the hypoactive delirium subtype patients. Furthermore, we found that the duration of delirium was significantly correlated to problems with memory and remembering names. In this study we concluded that ICU survivors who suffered from delirium during their ICU stay have a similar adjusted health related quality of life evaluation, but significantly more cognitive problems than those who did not suffer from delirium, even after adjusting for relevant covariates. In addition, the duration of delirium is related to long-term cognitive problems.

In **PART THREE** we focused on the *Prediction and Prevention of Delirium in Intensive Care Patients* and in **Chapter 8** we described the development and validation of a delirium prediction model for ICU patients. In this prospective study the model was developed in our hospital and subsequently validated in five intensive care units in the Netherlands (two university hospitals and three university-affiliated teaching hospitals). In this large study more than 3,000 patients were evaluated. The developed model consists of ten predictors that are readily available within the first 24 hours after patients' ICU admission. The developed prediction of delirium in ICU (PRE-DELIRIC) model showed a good performance, which remained good during the temporal and the external validation. Interestingly, the prediction of attending nurses' and physicians' was significantly less adequate compared with the PRE-DELIRIC model, illustrating the additional value of the model. The model allows for early delirium prediction and the initiation of preventive measures. The prediction model was then integrated in our patient data management system and implemented in our daily clinical practice.

In **Chapter 9** we evaluated the effects of prophylactic treatment of delirium using a low dose of haloperidol in ICU patients with a high (≥50%) predicted risk for delirium using the PRE-DELIRIC model, or ICU patients with a history of alcohol abuse or dementia. Primary outcome measures were delirium incidence, delirium free days without coma and 28-day mortality. Results of prophylactic treatment were compared with a historical control group and a contemporary group that did not receive haloperidol prophylaxis mainly due to non-compliance to the protocol during the implementation phase. We prospectively decided to evaluate our policy after 12 months. After 1 year, a total of 177 patients received prophylactic haloperidol treatment. The historical control group consisted of 299 patients and the contemporary group that was not preventively treated with haloperidol consisted of 59 patients. Delirium prophylaxis with haloperidol resulted in a significantly lower delirium incidence and more delirium free days. Cox-regression analysis adjusted

for sepsis showed a relative reduction of 20% of 28-day mortality in patients who received prophylactic treatment with haloperidol. Furthermore, haloperidol prophylaxis resulted in less ICU re-admissions and unplanned removal of tubes/lines. The 59 patients who were not treated during the intervention period showed similar results compared to the untreated control group, further substantiating these beneficial effects of haloperidol. Few side-effects were reported, all of which were evaluated not severe. We concluded that prophylactic treatment with low dose haloperidol in patients with a high risk for delirium exerts several beneficial effects.

In the last part of this thesis, **PART FOUR**, we examined the *Role of Biomarkers related to Delirium in Intensive Care Patients*. In **Chapter 10** we studied the effects of inflammation on brain function and cognitive function during experimental human endotoxemia. In 15 healthy male volunteers we measured levels of several cytokines, cortisol and brain specific proteins (BSP), the electroencephalography (EEG) changes and cognitive function tests (CFTs) prior to and during endotoxemia. The administration of 2 ng/kg E. Coli endotoxin resulted in a significant increase of circulating pro- and anti-inflammatory cytokines, and cortisol. The measured BSP remained within the normal range, but a statistically significant change in neuron specific enolase (NSE) and S100-β changed was observed. Quantitative EEG analysis showed a higher state of alertness which was related to the increase of cortisol. The observed CFTs changes during endotoxemia were found to be due to a practice effect. Furthermore we found that several biomarkers were correlated with improvement of some cognitive functions, i.e. of working memory and psychomotor speed capacity. No other significant correlations between cytokines, cortisol, EEG, CFT and BSP were found. We concluded that short-term systemic inflammation does not provoke or explain the occurrence of septic encephalopathy, but primarily results in an inflammation-mediated increase in cortisol and alertness.

In **Chapter 11** we determined plasma biomarkers in delirious and non-delirious ICU patients and examined the role of these biomarkers on long-term cognitive function to improve our insight in the relation between these markers and delirium.

In this exploratory observational study, ICU patients with or without delirium were divided in groups with ("inflamed") or without ("non-inflamed") evidence of an infection/SIRS to further elucidate the role of systemic inflammation. Within 24 hours following the onset of delirium, blood was obtained for biomarker analysis and in non-delirious patients we draw blood after a similar ICU length of stay compared to the group of delirious patients. Furthermore, 18 months after ICU discharge, a cognitive failure questionnaire (CFQ) was distributed to the ICU survivors. In this study 50 delirious and 50 non-delirious patients were included.

In inflamed delirious patients the proinflammatory cytokine interleukin (IL)-8 was independently associated with delirium, while IL-10 and amyloidβ1-42/40 were associated with non-inflamed delirious patients, as determined with multivariate regression analysis. Furthermore, levels of several amyloidβ forms, but not pro-inflammatory cytokines, human Tau or S100-β, were significantly correlated with self reported cognitive impairment 18 months after ICU discharge. These results suggest that proinflammatory cytokines are involved in the development of delirium in inflamed patients without long-term cognitive consequences, while amyloidβ is related to delirium in non-inflamed patients and associated with impaired cognitive functioning in the long-term. The results further support that the underlying mechanisms governing the development of delirium in inflamed patients differ from those in non-inflamed patients. The fact that elevated levels of amyloid-β correlated with long-term cognitive impairment suggests that development of delirium in non-inflamed patients may represent the first sign of a (subclinical) dementia process, but this needs to be confirmed in further studies.

In the final **Chapter 12** we summarized our findings and discussed the results of this thesis in view of several methodological issues and we elaborated on the clinical consequences of our results and aims for future research.

14

Samenvatting

Samenvatting

Delirium is een psycho-organische stoornis met een acuut begin gepaard gaande met bewustzijnstoornissen en een veranderde cognitie waarbij de verschijnselen kunnen fluctueren over de dag. De term psycho-organische stoornis houdt in dat er altijd een lichamelijke oorzaak zoals een infectie, dehydratie, verstoorde elektrolytenbalans of nierfalen, aan ten grondslag ligt aan het delirium.

We onderscheiden drie subtypen van delirium: een hyperactief subtype met symptomen van hyperalertheid of agitatie, een hypoactief subtype gekenmerkt door tekenen van hypoalertheid of lethargie en het gemengde subtype waarbij de hyper- en hypoactieve symptomen elkaar afwisselen.

Dit proefschrift had vier onderzoeksdoelen die werden behandeld in afzonderlijke delen:

- Verkrijgen van meer inzicht in de diagnose delirium bij intensive care (IC-) patiënten gebruikmakend van het delirium screeningsinstrument de 'Confusion Assessment Method-ICU' (CAM-ICU) en het onderzoeken of de diagnose delirium op een andere manier kan worden vastgesteld
- Vaststellen van de impact van delirium op verschillende korte- en lange termijn gezondheidsconsequenties
- Bepalen of delirium bij de IC-patiënten kan worden voorspeld en kan worden voorkomen
- Onderzoek naar de rol van (ontsteking) biomarkers bij IC-patiënten met delirium

In **DEEL EEN** hebben we ons gericht op de *Detectie van Delirium bij Intensive Care Patiënten*. Na een algemene en achtergrond beschrijving van delirium in **Hoofdstuk 1** beschrijven we in **Hoofdstuk 2** de implementatie van een op maat gemaakte strategie om de CAM-ICU in onze dagelijkse praktijk in te voeren. Deze strategie richtte zich op potentiële belemmeringen waarbij we gebruik hebben gemaakt van verschillende evidence based implementatie interventies. We evalueerden onze strategie aan de hand van de compliantie aan de CAM-ICU, de interbeoordelaarsbetrouwbaarheid, en kennis op het gebied van delirium van de IC-verpleegkundige als maat voor succes. Verder hebben we gekeken naar het effect van het gebruik van de CAM-ICU op het haloperidol gebruik, welke diende als vervangende maat voor de deliriumincidentie, voor en na de implementatie. In vier maanden was de compliantie aan de CAM-ICU, de kennis op het gebied van delirium en de interbeoordelaarbetrouwbaarheid significant toegenomen. Daarnaast stelden we vast dat meer patiënten behandeld werden met haloperidol,

maar voor een kortere periode en met een lagere dosering. Onze conclusie was dat het gebruik van deze op maat gemaakte implementatiestrategie heeft geleid tot een succesvolle introductie van de CAM-ICU in onze IC-praktijk en dat de belangrijkste doelstellingen snel waren bereikt. De observatie dat meer patiënten met haloperidol werden behandeld, maar met een lagere dosis en voor een kortere tijd na de succesvolle implementatie van de CAM-ICU suggereert dat delirium eerder werd gedetecteerd in een fase waarin de patiënt gevoeliger is voor de behandeling met haloperidol.

In **Hoofdstuk 3** beschrijven we een multicenter studie uitgevoerd op tien IC-afdelingen in Nederland waarbij onderzocht werd in welke mate de CAM-ICU delirium bij de patient kon vaststellen wanneer deze wordt gebruikt door IC-verpleegkundigen in de dagelijkse praktijk. Twee teams van drie delirium experts waaronder psychiaters, geriaters en neurologen bezochten de tien intensive care afdelingen twee keer. Op basis van cognitief onderzoek, het bestuderen van de medische dossiers en door gebruik te maken van de DSM-IV-TR criteria voor delirium, werden de patiënten door de expert teams aangemerkt als patiënten die wakker zijn en niet delirant, delirant, of comateus. Deze beoordeling diende als 'goud standaard' voor de diagnose delirium. De CAM-ICU uitgevoerd door de IC-verpleegkundigen bij 181 patiënten werd op deze manier vergeleken met deze 'goud standaard'. De CAM-ICU, wanneer gebruikt door IC-verpleegkundigen, presteerde duidelijk minder goed dan in de oorspronkelijke validatie studies uitgevoerd door onderzoeksverpleegkundigen. Hoewel de specificiteit van de CAM-ICU bij alle deelnemende centra hoog was, bleek de sensitiviteit van de CAM-ICU laag te zijn en er waren opvallende verschillen tussen de deelnemende centra. Bovendien, wanneer de data werden gestratificeerd bleek dat de sensitiviteit het laagst was in de hypoactieve delirium subgroep en de sensitiviteit was slecht in groep van neurologie patiënten. Onze bevinding dat de specificiteit van de CAM-ICU, zoals gebruikt in de dagelijkse praktijk, hoog lijkt te zijn, maar dat de sensitiviteit laag is belemmert vroege detectie van delirium door de CAM-ICU.

In het laatste hoofdstuk van deel één, **Hoofdstuk 4**, beschrijven we een prospectieve studie waarin we de mogelijkheid hebben onderzocht om een 'fingerprint' van delirium markers te vinden in de urine van de patiënten na een hartoperatie met behulp van urineproteomics. Hoewel urineproteomics onderzoek eerder met succes werd toegepast om nieuwe biomarkers te identificeren die geassocieerd zijn met diverse andere ziektebeelden, werd de waarde hiervan bij delirante IC-patiënten nog niet eerder onderzocht. Voor dit onderzoek werden IC-patiënten die na een hartoperatie een hyperactief delirium hadden ontwikkeld geïncludeerd en vergeleken met niet-delirante IC-patiënten na een hartoperatie. Urine werd verzameld binnen 24 uur na het ontstaan van het delirium. Matrix-assisted laser

desorptie/ionisatie-time of flight massaspectrometrie (MALDI-TOF MS) techniek werd toegepast om verschillen in de eiwituitscheiding in de urine te detecteren die mogelijk geassocieerd waren met delirium bij IC-patiënten. We includeerden 10 hyperactief delirium patiënten en 10 vergelijkbare niet-delirum patiënten na een hartchirurgische operatie. Er werden geen relevante verschillen in de urinaire excretie van eiwitten waargenomen. We concludeerden dat, gebruikmakend van de MALDI-TOF MS techniek, geen duidelijk hyperactief deliriumproteoom 'fingerprint' in de urine van IC-patiënten aantoonbaar is.

DEEL TWEE concentreerde zich op de *Impact van Delirium bij Intensive Care Patiënten* en in **Hoofdstuk 5** hebben we de incidentie en duur van delirium vastgesteld, per delirium subtype en per IC opnamediagnose. Daarnaast hebben we de korte termijn gevolgen van delirium onderzocht. In een grote prospectieve observationele studie werden alle volwassen IC-patiënten geïncludeerd die gedurende één jaar werden opgenomen op onze IC afdeling. Delirium werd vastgesteld met de CAM-ICU en patiënten met een delirium werden ingedeeld in hyperactief, hypoactief of in het gemengde delirium subtype. Als maat voor de korte termijn gevolgen gebruikten we de duur van de mechanische beademing, de incidentie van re-intubaties, incidentie van onbedoeld verwijderen van tubes en katheters, opnameduur op de IC en in het ziekenhuis, en de ziekenhuismortaliteit. In totaal werden 1613 patiënten geïncludeerd, waarvan 26% een delirium ontwikkelde tijdens de IC-periode. De incidentie in de groep neurochirurgische patiënten (10%) en hartchirurgische patiënten (12%) was het laagst; de incidentie was hoger in de groep medische patiënten (40%) en het hoogst in de groep neurologie patiënten (64%). Het gemengde delirium subtype kwam bij IC-patiënten het meest frequent voor en het hyperactieve subtype het minst. De mediane duur van delirium was twee dagen en de duur was significant langer in de groep patiënten met het gemengde delirium subtype. Wat betreft de korte termijn gevolgen stelden we vast dat mechanische beademing bij deliriumpatiënten vaker noodzakelijk was, de beademingsduur langer was en deze patiënten vaker tubes en katheters verwijderden. Ook was de opnameduur op de IC en in het ziekenhuis langer en patiënten met een delirium hadden, na correctie voor ziekte-ernst, een zes keer grotere kans te overlijden vergeleken met niet-delirante IC-patiënten. We concludeerden dat de deliriumincidentie op een gemengde IC afdeling hoog is en verschilt per IC opnamediagnose en per delirium subtype. Patiënten met delirium hadden significant meer last van nadelige korte termijn gevolgen, onafhankelijk van de ziekte-ernst. Dit was het meest uitgesproken voor het gemengde subtype van het delirium.

In **Hoofdstuk 6** onderzochten we of het toevoegen van de diagnose delirium,

aanwezig binnen 24 uur na IC opname, als een extra variabele aan de ziekte-ernst score, de APACHE-II, de nauwkeurigheid van de sterfteschatting van de APACHE-II zou kunnen verbeteren. In deze prospectieve cohort studie werden 2116 volwassen patiënten gescreend op delirium en 1740 patiënten werden geïncludeerd voor analyse. Hiervan waren 332 (19%) patiënten al delirant tijdens de opname op de IC of binnen 24 uur na IC opname. Wij stelden vast dat delirium significant was geassocieerd met ziekenhuissterfte. Echter, de voorspellende waarde van de APACHE-II verbeterde niet na toevoegen van delirium, zowel in de totale groep patiënten als in de subgroep zonder cardiochirurgische patiënten. We kwamen tot de conclusie dat, hoewel delirium een significante voorspeller is van sterfte bij IC-patiënten, het toevoegen van delirium als een extra variabele aan het APACHE-II model, de voorspellende waarde van het model niet verbeterde.

In **Hoofdstuk 7** onderzochten we de impact van delirium op de lange termijn gezondheidsgerelateerde kwaliteit van leven en het cognitief functioneren van de IC- overlevenden. In deze prospectieve follow-up studie werden na een mediane duur van 18 maanden na IC ontslag, kwaliteit van leven vragenlijsten verstuurd naar 1292 IC overlevenden waarvan 21% met, en 79% zonder delirium tijdens hun IC opname. We gebruikten de SF-36v1 (SF-36) vragenlijst, de CIS-vermoeidheid en de CFQ (cognitieve vragenlijst) om de door de patiënten ervaren kwaliteit van leven en hun cognitief functioneren te evalueren. In totaal reageerden 915 (71%) patiënten, waarvan er 171 (19%) patiënten delirant waren geweest tijdens de IC opname. Na correctie voor verschillende covariabelen, werden geen verschillen gevonden tussen delirium en niet-delirium overlevenden in de SF-36 en de CIS-vermoeidheid scores. Echter, overlevenden die een delirium hadden doorgemaakt meldden significant vaker dat ze vergissingen op sociaal gebied maakten en hun algemene cognitieve functie was significant slechter in vergelijking met overlevenden die niet delirant waren geweest tijdens de IC-opname. Overlevenden die een gemengd of een hyperactief subtype delirium hadden doorgemaakt scoorden aanzienlijk slechter op het domein geestelijke gezondheid in vergelijking met de overlevenden na een hypoactief delirium subtype. Verder vonden we dat de duur van een delirium sterk was gecorreleerd met geheugenproblemen en het onthouden van namen. In deze studie concludeerden we dat de IC overlevenden die delirant waren geweest tijdens hun IC opname een vergelijkbare score hadden op de kwaliteit van leven, maar hadden aanzienlijk meer cognitieve problemen dan degenen die niet delirant waren geweest, ook na correctie voor relevante covariabelen. Daarnaast was de duur van het delirium gerelateerd met de lange termijn cognitieve problemen.

In **DEEL DRIE** hebben we ons gericht op de *Voorspelling en Preventie van Delirium bij Intensive Care Patiënten* en in **Hoofdstuk 8** beschrijven we de ontwikkeling en

validatie van een delirium predictiemodel voor IC-patiënten. In een prospectieve studie werd het model ontwikkeld in ons ziekenhuis en vervolgens gevalideerd op vijf intensive care units (twee universitaire ziekenhuizen en drie grote regionale ziekenhuizen) in Nederland. In deze grote studie werden ruim 3000 patiënten geïncludeerd. Het ontwikkelde model bestaat uit tien voorspellers/predictors die eenvoudig beschikbaar zijn binnen 24 uur na IC-opname. Het IC delirium predictie (PRE-DELIRIC) model had bij de ontwikkeling ervan een goede voorspellende waarde, die goed bleef tijdens de interne en de externe validatie. Interessant is dat de voorspelling van de zorgverleners (verpleegkundigen en artsen) significant minder goed was in vergelijking met het PRE-DELIRIC model, wat aantoont dat het model van toegevoegde waarde is. Het model zorgt voor een vroege deliriumvoorspelling en het kunnen initiëren van preventieve maatregelen. Het PRE-DELIRIC model werd vervolgens geïntegreerd in ons patiënt-data-management-systeem en geïmplementeerd in onze dagelijkse klinische praktijk.

In **Hoofdstuk 9** onderzochten we de effecten van delirium profylaxe met een lage dosis haloperidol bij IC-patiënten met een voorspelt hoog risico (≥ 50%) op het ontwikkelen van delirium zoals vastgesteld met het PRE-DELIRIC model, en IC-patiënten met een voorgeschiedenis van alcoholmisbruik of dementie. Primaire uitkomstmaten waren optreden van delirium, aantal deliriumvrije dagen zonder coma, en 28-dagen mortaliteit. De resultaten van profylactische behandeling met haloperidol werden vergeleken met een historische controlegroep en een groep patiënten die geen haloperidol profylaxe hadden gehad tijdens de interventieperiode, wat vooral te wijten was aan het niet naleven van het preventieprotocol tijdens de implementatiefase. Vooraf werd afgesproken het preventiebeleid na 12 maanden te evalueren. In totaal werden 177 patiënten profylactische behandeld met haloperidol. De historische controlegroep bestond uit 299 patiënten en de niet preventief behandelde interventiegroep bestond uit 59 patiënten. Deliriumprofylaxe met haloperidol resulteerde in een significant lagere deliriumincidentie en toename van het aantal deliriumvrije dagen. Cox-regressie analyse, gecorrigeerd voor sepsis, liet een relatieve mortaliteitsreductie zien van 20% op de 28-dagen mortaliteit bij patiënten die profylactisch waren behandeld met haloperidol. Bovendien resulteerde haloperidol profylaxe tot minder IC heropnames en onbedoeld verwijderen van tubes en katheters. De 59 patiënten die niet preventief werden behandeld tijdens de interventieperiode lieten vergelijkbare resultaten zien als de onbehandelde controle groep, hetgeen suggereert dat de positieve effecten vastgesteld in de behandelde groep veroorzaakt worden door het preventief behandelen met haloperidol en niet door een tijdsafhankelijke invloed. Er werden weinig bijwerkingen gemeld, die bovendien allemaal als niet ernstig werden geëvalueerd. We concludeerden dat profylactische behandeling met een

lage dosis haloperidol bij patiënten met een hoog risico op delirium resulteert in vooral gunstige effecten.

In het laatste deel van dit proefschrift, **DEEL VIER**, onderzochten we de *Rol van Biomarkers gerelateerd aan Delirium bij Intensive Care Patiënten*. In **Hoofdstuk 10** hebben we de effecten bestudeerd van een ontsteking op de hersenfunctie en de cognitieve functie tijdens experimentele endotoxinemie bij mensen. Bij 15 gezonde mannelijke vrijwilligers hebben we waarden bepaald van verschillende ontstekingseiwitten (cytokines), het stress-hormoon cortisol en enkele hersenspecifieke eiwitten (HSE), de elektro-encefalografie (EEG) veranderingen en cognitieve functietesten (CFT's) voorafgaand aan, en tijdens de endotoxinemie. De toediening van 2 ng/kg E. Coli endotoxine resulteerde in een significante stijging van de circulerende pro-en anti-inflammatoire cytokines en het cortisol. De gemeten HSE bleven allen binnen de normaal waarde, maar er was een statistisch significante verandering te zien van het neuron specifiek enolase (NSE) en S100-β. Kwantitatieve EEG analyse liet een verhoogde staat van alertheid zien, die was gerelateerd aan de toename van het cortisol. De waargenomen CFT's veranderingen tijdens endotoxinemie bleken te worden veroorzaakt door een leereffect. Verder vonden we dat een aantal biomarkers waren gecorreleerd met verbetering van een aantal cognitieve functies, dat wil zeggen met het werkgeheugen en psychomotorische snelheid van reageren. Er werden geen andere significante correlaties tussen cytokines, cortisol, EEG, CFT en HSE gevonden. We concludeerden dat de kortdurende systemische ontsteking geen septische encephalopathie kon provoceren of het ontstaan ervan kon verklaren, maar dat de kortdurende systemische ontsteking vooral resulteerde in een ontsteking-gemedieerde toename van cortisol en alertheid.

In **Hoofdstuk 11** hebben we biomarkers in bloedplasma bepaald bij delirante en niet delirante IC-patiënten en onderzochten we de rol van deze biomarkers op lange termijn cognitieve functies, om ons inzicht te verbeteren in de relatie tussen deze markers en delirium. In deze exploratieve observationele studie werden de IC-patiënten met of zonder delirium verdeeld in groepen met ("inflammatie") of zonder ("niet-inflammatie") aanwijzingen van een infectie/ontsteking om verder de rol van een systemische ontsteking te ontrafelen. Binnen 24 uur na het ontstaan van het delirium, werd bloed afgenomen voor analyse van biomarkers en van niet-delirante patiënten werd bloed afgenomen na een vergelijkbare IC opnameduur als die van de patiënten met een delirium. Verder werd, 18 maanden na IC ontslag, een Cognitive Failure Questionnaire (CFQ) toegezonden aan de overlevenden. In deze studie werden 50 delirante en 50 niet-delirante IC-patiënten geïncludeerd. Bij de deliriumpatiënten met inflammatie was het pro-inflammatoire cytokine

interleukine (IL)-8 onafhankelijk geassocieerd met het optreden van delirium, terwijl IL-10 en amyloidβ 1-42/40 waren geassocieerd met delirium bij patiënten zonder inflammatie, beide bepaald middels multivariaat regressie analyse. Verder waren de waarden van verschillende amyloidβ vormen (maar niet de pro-inflammatoire cytokines, het menselijke Tau of S100-β) significant gecorreleerd met zelf-gerapporteerde cognitieve stoornissen, 18 maanden na IC ontslag. Deze resultaten suggereren dat pro-inflammatoire cytokines betrokken zijn bij de ontwikkeling van het delirium bij patiënten met inflammatie en dat dit geen lange termijn cognitieve gevolgen veroorzaakt, terwijl amyloïdeβ is gerelateerd aan delirium bij patiënten zonder inflammatie geassocieerd met een verminderd cognitieve functioneren op de lange termijn. Deze resultaten ondersteunen het idee dat de onderliggende mechanismen van de ontwikkeling van delirium bij IC-patiënten met inflammatie anders is vergeleken met IC-patiënten zonder inflammatie. Het feit dat de verhoogde waarden van amyloidβ correleert met lange termijn cognitieve stoornissen suggereert dat de ontwikkeling van het delirium bij patiënten zonder inflammatie het eerste teken kan zijn van een (subklinisch) dementieel proces, maar dit moet bevestigd worden in vervolgstudies.

In het laatste **Hoofdstuk 12** hebben we onze bevindingen samengevat en de resultaten van dit proefschrift besproken in het licht van een aantal methodologische zaken en zijn we ingegaan op de klinische consequenties van onze resultaten en doelen voor toekomstig onderzoek.

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List of abbreviations

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Aβ1-42/40	Amyloidβ 1-42 and 1-40
AβN-42/40	Amyloidβ truncated-42 and 1-40
AD	Alzheimer disease
APACHE-II	Acute physiology and chronic health evaluation-II
AUC	Area under the receiver operating characteristics curve
BSP	Brain specific proteins
CABG	Coronary artery bypass graft
CAM-ICU	Confusion assessment method – intensive care unit
CF	Cognitive function
CFQ	Cognitive failure questionnaire
CI	Confidence interval
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DSM-IV	Diagnostic and statistical manual of mental disorders-IV
EEG	Electroencephalography
GFAP	Glial fibrillary acidic protein
HL-test	Hosmer-Lemeshow test
HNP	Human neutrophil protein-1
IQCODE-sf	Informant questionnaire on cognitive decline short form

IQR	Interquartile range
IL	Interleukin
LPS	Lipopolysaccharide
MALDI-TOF MS	Matrix assisted laser desorption / ionisation time of flight mass spectrometry
MCP	Monocytes chemotactic protein-1
MDRD-GFR	Modification of diet in renal disease – glomerular filtration rate
MIF	Macrophage migration inhibitory factor
NSE	Neurospecific enolase
OR	Odds ratio
PASAT	Paced auditory serial addition test
RASS	Richmond agitation sedation score
S100-β	S100 calcium binding protein-β
SDT	Digit symbol test
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
STAI	State trait anxiety inventory
TNF-α	Tumor necrosis factor-α
WAIS-III	Wechsler adult intelligence scale III

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Dankwoord
Curriculum Vitae

Dankwoord

Na ruim vier jaar noeste arbeid kan het hoofdstuk promoveren worden afgesloten. Het is een leuke, interessante en vooral leerzame weg geweest. Maar deze weg bewandel je nooit alleen. En dat kan ook niet. Hierbij word je begeleid en gesteund (direct en indirect) door vele mensen met ieder hun eigen inbreng en bijdrage. Hun bijdrage is voor mij altijd zeer waardevol geweest. Hoewel ik dit misschien niet altijd even duidelijk vertel, ben ik eenieder hier zeer dankbaar voor. Nu krijg ik de kans om mijn dank op papier te zetten zodat het ook vastligt. Mocht ik toch nog iemand vergeten zijn dan excuses hiervoor.

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Paranimfen **Marius** en **Frank**; ik vind het werkelijk bijzonder dat mijn twee beste vrienden vandaag naast me staan tijdens deze belangrijke dag. De start van onze vriendschap dateert alweer van enige tijd geleden. Voor Marius al tijdens onze inservice A-opleiding in Boxmeer in 1983. Hier beleefden we gouden tijden in de 'huiskamer', biljarten bij 'schele Herman', de DOKA om foto's te ontwikkelen, alle ontgroeningen die we uitvoerden of waar we aan mee hielpen etcetera. Prachtig. Maar ook bij belangrijkere werkzaamheden als in de leerlingenraad en de ondernemingsraad. De vriendschap tussen ons vieren, met jouw vrouw Anja en mijn vrouw Lilian, is altijd in stand gebleven en zelfs nog intensiever geworden. Recentelijk hebben we ons 25-jarig jubileum gevierd; op naar de volgende 25 jaar.

Frank, wij kennen elkaar ook alweer 15 jaar en onze vriendschap is ontstaan tijdens onze samenwerking op de AOV-IC. Het klikte meteen, ook later met Alice erbij. Het was altijd een gezellig samenzijn met veel wederzijdse belangstelling voor elkaar, meestal onder het genot van een heerlijk glas wijn. Toen ik begon als onderzoeker wist jij het meteen: 'dit gaat jou glansrijk lukken', en ik wist meteen dat jij het absoluut zou maken als fotograaf toen jij je uniform inruilde om vakfotograaf te worden. Het is je gelukt, en zie daar, een prachtige door jou gemaakte coverfoto op mijn boekje.

Verder wil ik alle medeauteurs bedanken die het mogelijk hebben gemaakt om de delirium onderzoeken uit te voeren. De samenwerking met meerdere centra, onder andere met Utrecht (Arjen Slooter), Leeuwarden (Michael Kuiper), Apeldoorn (Peter Spronk), Amsterdam (Peter van der Voort), Den Bosch (Koen Simons en Peter de Jager) zijn zeer belangrijk en waardevol voor me geweest, en nog.

En niet te vergeten, en zeker niet op de laatste plaats, ook mijn (schoon-)ouders, broer, zwagers, schoonzussen, neven en nichtjes en andere niet genoemde vrienden. Jullie wil ik ook bedanken voor jullie interesse en begrip, vooral als ik weer eens iets vergeten was. Of geen tijd had omdat ik nog moest werken om onderzoeksgegevens te verzamelen of data te analyseren of artikelen te schrijven. **Gerco** en **Agnes** dank voor alle heerlijke en gezellige etentjes met jullie, gecombineerd met jullie interesse en support voor en tijdens mijn promotie. **Ronald**, dank voor de vele uren ontspanning waar jij aan bijdroeg tijdens het racefietsen en ATB-en. Hopelijk volgen nog vele tochten.

Lieve **Lilian**, het beste moet je altijd voor het laatste bewaren. Ik kan het niet vaak genoeg zeggen; zonder jou was dit zeker nooit gelukt. Ik ben je eeuwig dankbaar. Al tijdens mijn studie Verplegingswetenschap zorgde jij ervoor dat ik de ruimte kreeg om te studeren en hierna ook nog eens tijdens mijn promotietraject kreeg ik alle tijd en ruimte. Je kwam met een subliem voorstel; laten we voor iedere publicatie voor je proefschrift uit gaan eten. Zo heb ik warme herinneringen overgehouden aan etentjes bij onder andere De Schat (Nijmegen), Puur (Berg en Dal), Kaatje bij de Sluis (Blokzijl) en last but not least, Bridges (Ubud, Bali). Mede hierdoor vond jij het ook beslist niet bezwaarlijk dat er iets meer hoofdstukken in mijn proefschrift staan.

Altijd was jij mijn sociale antenne en agenda, zorgde dat thuis alles op rolletjes liep, regelde en bereidde onze vakanties voor en deed alles wat ik nu vergeet. Het is gewoon teveel om op te noemen. DANK, DANK en DANK… we fietsen samen een mooie toekomst tegemoet.

Curriculum vitae

Mark van den Boogaard werd geboren op 8 februari 1965 in Nijmegen. Na zijn middelbare school (Merletcollege te Cuijk) startte hij in 1983 met de Verpleegkundige inservice-A opleiding in het Maasziekenhuis te Boxmeer gevolgd door Militaire Dienstplicht in het Militair Revalidatie Centrum te Doorn. Vervolgens rondde hij succesvol de Coronary Care Unit opleiding af in het Westeinde Ziekenhuis te Den-Haag (1988-1990), gevolgd door de intensive care opleiding in ziekenhuis de Weezenlanden te Zwolle (1990-1992). In 1996 ging hij werken als IC verpleegkundige op de hartchirurgische intensive care unit van het UMC St Radboud te Nijmegen. Van 1994 tot 2000 was hij daarnaast tevens gastdocent hartritme-geleidingsstoornissen aan het Deltion college te Zwolle en St. Antonius Academie te Nieuwegein en ambulance verpleegkundige bij de GG&GD te Nijmegen van 1995 tot 2000.

Nadat hij zijn colloquium doctum had behaald in 1998 volgde hij een wiskunde opleiding aan het James Boswell instituut van de Universiteit Utrecht. Vervolgens studeerde hij Gezondheidswetenschappen afstudeerrichting Verplegings-wetenschap aan de Universiteit Utrecht en behaalde in 2005 zijn masters diploma. Hij studeerde af op een gerandomiseerde studie over subacute wonden waarbij het effect op de wondgenezing werd bestudeerd van twee wondbehandelingsmethoden.

In 2007 werd hij aangenomen als promovendus/wetenschappelijk onderzoeker op de Intensive Care. Het samenwerkingsverband tussen de afdelingen Intensive Care (prof. Hans van der Hoeven, prof. Peter Pickkers) en de afdeling IQ Healthcare (prof. Theo van Achterberg, dr. Lisette Schoonhoven) heeft geresulteerd in de totstandkoming van dit proefschrift over Delirium bij Intensive Care Patiënten. Tijdens zijn onderzoeksperiode won hij de prijs voor beste mondelinge presentatie bij het NVIC-congres 2010 over het delirium predictie model. Verder waren twee van zijn artikelen genomineerd voor de Anna-Reynvaan wetenschapsprijs in 2010 en in 2011.

Naast zijn werk als wetenschappelijk onderzoeker is Mark bestuurslid van Venticare en het tijdschrift Kritiek en is lid van de programmacommissie van Venticare, lid en secretaris van het Delirium Consortium Intensive Care, Scholar of the European Academy of Nursing Science, extern lid van de kenniskring van het lectoraat Acute en Intensieve Zorg aan de HAN, lid van de European Delirium Association en is hij lid van de Working Group Postoperative Delirium and Cognitive Dysfunction van de European Society of Intensive Care Medicine.

Na zijn promotie zal Mark zich verder bekwamen in de epidemiologie (onder andere door het volgen van de Summer Course Epidemiology in de V.S. en van de Masteropleiding Epidemiologie aan de Radboud Universiteit Nijmegen) en verbonden blijven aan de afdeling intensive care als wetenschappelijk onderzoeker.

Mark is getrouwd met Lilian Peters en woont in Nijmegen.

IC Research

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